present concepts

in Internal Medicine

VOL IV No 8 August 1971

UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
Department of Medicine	2b. GROUP

3. REPORT TITLE

PULMONARY DISEASES SYMPOSIUM

VOL IV No 8, AUGUST 1971, PRESENT CONCEPTS IN INTERNAL MEDICINE* (See Item #11)

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*
Symposium (medical) August 1971

5. AUTHOR(S) *(First name, middle initial, last name)*
Mays, Edward E. (Guest Editor). Contributors: Hinshaw HC, Chandler EF, Murray JF, Mays EE, Lipschultz AS, Hamaker WR, Ziporin P.

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
August 1971	112 (pp 593-704)	230

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N/A	N/A
b. PROJECT NO.	
c.	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)* N/A
d.	

10. DISTRIBUTION STATEMENT
The distribution of this document is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
*Twelve symposia per year form a volume. Each symposium is on a different specialty in internal medicine.	LETTERMAN GENERAL HOSPITAL Presidio of San Francisco, Calif 94129

13. ABSTRACT

This issue of Present Concepts is devoted to an attempt at defining the rapidly evolving role of the chest physician in medical practice today. Some of the many topics which reflect some of the dynamism that now prevades the thoughts of pulmonary physician are presented. Beginning with the provocative editorial giving interpretation to prevailing trends in pulmonary defenses against infection, the symposium continues with nine other articles and concludes with the exclamation "Blood Gases are Pulmonary Function Tests!".

In this group of articles one sees that chronic obstructive pulmonary disease has forged forward as the present challenge. In addition to the two mentioned above, the titles of the other articles provide insight into the scope of the symposium: "The impact of the decline of tuberculosis on the role of the chest physician", "'Shock lung'", "Chronic obstructive pulmonary disease. The present challenge", "Control of ventilation in respiratory failure", "Hospital-acquired gram-negative pneumonias", "Sarcoidosis. Etiology and treatment", "Newer chest diagnostic techniques" (as reviewed by a thoracic surgeon), and "Pulmonary defenses against infection".

DD FORM 1 NOV 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

UNCLASSIFIED

Security Classification

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
PULMONARY DISEASES						
LUNG DISEASES						
LUNG COMPLIANCE						
RESPIRATION						
PNEUMONIA, Hospital-acquired, gram-negative.						
BLOOD GAS ANALYSIS						
PULMONARY CIRCULATION						
VENTILATION-PERFUSION						
THORACIC, diagnositic techniques						
[redacted]						
SARCOIDOSIS, ETIOLOGY						
TREATMENT						

PRESENT CONCEPTS IN INTERNAL MEDICINE

GUEST EDITOR FOR AUGUST 1971

LTC Edward E. Mays, MC
Chief, Pulmonary and
Infectious Disease Service

ASSISTANT EDITOR

Lottie Applewhite, M.S.

EDITORIAL BOARD

LETTERMAN GENERAL HOSPITAL
Presidio of San Francisco, California 94129

PRESENT CONCEPTS IN INTERNAL MEDICINE

VOLUME IV *August 1971* Number 8

PULMONARY DISEASES SYMPOSIUM

CONTENTS

FORTHCOMING SYMPOSIA . . .

NEPHROLOGY

NEUROLOGY

MEDICAL WRITING and JOURNALISM

FOREWORD

This issue is devoted to an attempt at defining the rapidly evolving role of the chest physician in medical practice today. In doing so, we have purposely selected some of the many possible topics which more forcefully reflect some of the dynamism which has now pervaded the thoughts of pulmonary physicians. Concepts of all the diseases, approaches and techniques herein discussed are rapidly changing, and as such are subject to highly individualistic or provincial interpretation or criticism, a calculated risk which we are willing to accept, if motivation of thought or stimulation of constructive effort ensues.

The provocative, pertinent editorial by Doctor Hinshaw, one of our three guest contributors, is an example of our intent to question and give our interpretation of the prevailing trends. The succinct review of "Shock Lung" by Doctor Murray, another guest contributor, and Letterman's newest Chest Consultant, hardly hints at the painstaking difficulties experienced in arriving at a definition of this relatively new syndrome. The realization that the same syndrome is titled "adult respiratory distress syndrome", or "progressive pulmonary consolidation", among other things, at other teaching centers attests to the previous quandry experienced by chest physicians. The evaluation of the syndrome's definition, several etiologies, and present therapy serve as a worthy example of the progressive attitudes, the tenacious endeavor, and the enlightened query which pervade the thinking in chest medicine today. That this evolution has affected our sister disciplines is clearly reflected in the apt summarization of "Newer Chest Diagnostic Techniques" by Doctor Hamaker, one of Letterman's surgeons.

Doctor Bruce Chandler has admirably set the tone for this symposium by his personalized outline of the blossoming commitment of the chest physician into other priorities, coincidental with the declining incidence of tuberculosis. This point is of such gravity, and the causative changes have been as mercurial, that there presently exists something of a "generation gap" between younger and older chest physicians.

Foreword

Our staff has attempted to define further some of the clear and not-so-clear challenges which now confront the chest physician. Doctor Lipschultz has superbly reviewed an old nemesis — sarcoidosis; and a more insidious problem — respiratory failure. Our youngest member, Doctor Ziporin, a fledgling chest fellow, has brought us to the cellular and metabolic level in infectious diseases, one of our greatest problem areas. Finally, the guest editor has dared to include the results of some clinical research on blood gases in which the laborious present concepts of pulmonary function testing are challenged.

Whatever the end result, the presentation of this symposium has been a learning experience for us.

LTC EDWARD E. MAYS, MC
Guest Editor

EDITORIAL

H. Corwin Hinshaw, M.D., Ph.D.

Clinical Professor of Medicine
University of California, School of Medicine, San Francisco, and Consultant, Pulmonary and Communicable Disease Service, Letterman General Hospital

Tuberculosis has been a constant companion of the human race since the beginning of the race, and before. Tuberculosis must have been a powerful force in evolution of the human race; survival fitness against disease being a selective factor equal to survival fitness against the other forces of Nature. Tuberculosis was incurable until the present generation. Now it is surely a curable disease; but this does not mean that all cases are curable or that failure to cure is a fault of the treatment administered.

The response of tuberculosis to treatment with antimicrobial drugs is comparable to that of any other infectious disease so treated, but the nature of the organism and the pathological consequences of the infection must be considered. The physician may approach the treatment of a tuberculous infection with the same confidence that he enjoys in treating a pneumococcus infection if his understanding of the bacteriology and the pathology of the two conditions is equally clear. Unfortunately tuberculosis is an extremely complicated disease.

When tuberculosis patients were neatly ensconced in sanatoriums these problems were of little general medical interest. But times are changing; sanatoriums are being abandoned, general hospitals are accepting cases of tuberculosis and

general physicians are being encouraged to treat under ambulatory conditions. To some of us these trends are a cause for anxiety; especially are we anxious about the ambulatory treatment of communicable disease.

The statement is made (quite without foundation) that the sputum positive person is harmless if he is receiving isoniazid. This is an unfounded extrapolation of the fact that soon after starting treatment, many (but not all) patients cease to cough and expectorate. Others - many others - continue to spread pathogenic bacilli and cannot be regarded as noncontagious during the first few months of treatment. It is only by careful bacteriologic examinations that the unsafe individuals may be recognized.

Unfortunately many general hospitals do not have the facilities and the skills to identify tubercle bacilli, to determine their susceptability to the several antibacterial drugs, to determine if a given patient is a rapid inactivator of isoniazid, to distinguish Mycobacterium tuberculosis from some similar Mycobacteria.

Unfortunately many general hospitals must enforce room isolation for patients with communicable disease. When treatment requires long periods of isolation these restrictions become nearly unbearable. For the patient, for the physician and for the family general hospital treatment is often a poor substitute for sanatorium treatment. There are outstanding exceptions; general hospitals with all the facilities and all the skills necessary to deal with the complex problems presented by many tuberculosis patients.

Many patients who require treatment for tuberculosis do not require isolation during much or all the period of treatment. But there are many others who must be restricted for prolonged periods. It is the opinion of most experienced clinicians that any person who expectorates tubercle bacilli must be regarded as a hazard to the health of the public.

Ambulatory treatment of tuberculosis, even from the beginning of therapy, is the obvious choice of the patient

when a choice is offered to him. His family will also make this choice and perhaps his physician will prefer not to relinquish control. Surely the tax payers and their political representatives will recognize the financial advantages of ambulatory care. However, none of these would make such a choice if a serious risk could be avoided by a period of institutional care for several weeks or even a few months. Thus the problem becomes one of distinguishing the safe from the unsafe individuals; a task calling for excellent laboratory facilities, skillful radiologists and knowledgeable clinicians. Most larger medical centers can provide these services but the usual general hospital cannot.

Tuberculochemotherapy is rarely simple and often difficult. The physician needs substantial knowledge about such drugs as streptomycin, aminosalicylate, isoniazid, ethambutol, rifampin, ethionamide and pyrazinamide. Some of these have lethal potentialities and all are capable of producing serious side effects, often of unique character.

Sanatoriums should not be abandoned unless better facilities can be provided elsewhere. Medical centers should cultivate interest in tuberculosis and provide special facilities for long-term treatment when it is required. Most important is the development of bacteriologic and physiologic laboratory facilities to deal with all aspects of tuberculosis. Ambulatory care should be encouraged, but only after it is reasonably certain that substantial risk has been eliminated.

Tuberculosis remains one of the most important chronic infectious diseases, especially among the less favored classes of society. In underdeveloped countries it constitutes a serious handicap to full development. Political leaders spend vast sums to protect their people from potential human enemies, but rarely have the courage - or the knowledge - to expend similar amounts of money to protect citizens from microbial enemies. Is it possible that within this decade the political consequences of illness will receive appropriate recognition?

The first thing to do in life is to do with purpose what one proposes to do.

—Pablo Casals

THE IMPACT OF THE DECLINE OF TUBERCULOSIS ON THE ROLE OF THE CHEST PHYSICIAN

Bruce F. Chandler, M.D., COL, USA (Retired)*

In the not too distant past, the term phthisiologist, or specialist in phthisis, another name for tuberculosis, was a common synonym for chest physician. Certainly, until World War II, and even some years afterwards, pulmonary disease received little attention except those aspects related to tuberculosis or changes within the lungs secondary to heart disease. Numerically, this was certainly the way that the situation should have been because, only a half century ago, tuberculosis was the nation's number one killer disease. Now, it is only number twenty. The number of deaths for 1969, which are the latest figures available from the Federal Center for Disease Control in Atlanta, was 5,340. This compares with 10,866 tuberculosis deaths as recently as 1960 and with figures in the 100,000's four to six decades ago. During the year of 1970, new active cases in tuberculosis reported in the United States reached an all time low of 37,187, as compared with 55,494 in 1960. To keep things accurate, it should be mentioned, however, that in 1969, the most recent year for which figures are available, the total of known active cases in the United States was 114,620, of which 5,500 involved relapses.

Another way of assessing the decline of tuberculosis is by looking at the bed situation in hospitals. The number of non-Federal hospitals with ten or more beds for tuberculosis

* Formerly, Chief, Pulmonary and Communicable Disease Service, Letterman Army Hospital
Presently, Member, Department of Internal Medicine, Drummond Medical Group and Director of Respiratory Care, Ridgecrest Community Hospital, Ridgecrest, California

patients has declined by more than a third in the past decade, from 345 in 1961 to 206 in 1970. The number of beds assigned for tuberculosis patients in these facilities has been reduced even more dramatically, from 40,820 to 14,827. In Federal hospitals, tuberculosis patient census has declined by 64 percent (from 8,036 to 2,887) over this ten year period. We might also compare the tuberculosis census at Fitzsimons General Hospital in 1948 and 1971. The respective figures are over 2,000 in the earlier year and approximately 75 at the present time.

Therefore, even though we must maintain careful vigilance about tuberculosis in this country, it is obvious that the present day chest physician cannot be only a specialist in tuberculosis, and still survive and have something to do. I must hasten to add, however, at this time that the chest physician must guard against being so forgetful or fearful about tuberculosis threat that, should he encounter a patient with the disease, he will not panic and immediately ship the patient off to the "county hospital" or the "san". Instead, he must be able to care for the patient in the general hospital setting, and not neglect the careful contact work that is so vital, and not neglect careful skin testing programs.

Beginning after World War II particularly, an accelerated interest in pulmonary diseases developed. This was related to many factors, including the awareness of arising incidence of lung cancer, atmospheric pollution, and the development of improved methods to diagnose obstructive pulmonary disease and follow their therapy and progression. Epidemiologic studies revealed a high incidence of pulmonary disease such as emphysema and chronic bronchitis in smokers compared to nonsmokers in various populations. Climatic factors, hereditary predisposition, age and the coexistence of other diseases were all linked to pulmonary disease. The pulmonary physician now found himself, as well as the tuberculosis patient, not necessarily isolated to specialized hospitals. Instead, nowadays, the chest physician finds himself an integral part of every hospital staff and participates much more fully in the medical education of interns and residents, as well as participating more fully in all phases of community medicine.

I think it might be fitting at this time to mention that in the May 1971 issue of Chest, the official publication of the American College of Chest Physicians, there is not a single article connected with tuberculosis. Instead, the articles are all connected with the new practice of critical care medicine, and such titles are noted as "Respiratory Care Units and Coronary Care Units" and "The Coronary Care Unit in the 1970s", Essentials of an Intensive Respiratory Care Unit" and Cardiac Pacing". I think that this illustrates the close connections that the chest physician now has with Intensive Care Units and illustrates also the fact that the heart and lungs are both very important in chest medicine, and that the chest physician must also know a great deal about cardiology and work closely with cardiologists. In many places now, the chest physician may find himself the director of Respiratory Care Units or of Intensive Care Units. He also will find himself working closely, not only with cardiologists, but also with anesthesiologists. I think that Dr. Thomas L. Petty of Denver sums it up nicely with his editorial in the same issue of Chest entitled "Respiratory Care is Mod!".

Another journal dear to the hearts of the chest physicians is The American Review of Respiratory Disease. This was formerly called The American Review of Tuberculosis and Pulmonary Diseases. I think that the decline of tuberculosis is also well demonstrated when the official journal of the American Thoracic Society, which is the medical section of the National Tuberculosis and Respiratory Disease Association, went so far as to drop the word tuberculosis from the juornal's title. Actually, our own national association, until recently, was indeed called the National Tuberculosis Association (NTA). In order to attract all physicians and all other paramedical and volunteer personnel, recently the words respiratory disease were added to the title and the famous "Christmas Seal Association" now has the initials NTRDA. At any rate, this April 1971 issue of this journal has only one title which mentions the word tuberculosis and this was "Rifampin in Initial Treatment of tuberculosis. A U.S. Public Health Service Tuberculosis Therapy Trial". Of the total of seventeen articles in this particular issue, three are concerned with Mycobacteria of other types; one is entitled "Tuberculin Sensitivity Eight to Fifteen Years after BCG Vaccination" and one is in reference to tuberculous infection possibilities in sarcoidosis

and asthmatic patients. The eleven other articles do not discuss any aspect remotely connected with tuberculosis.

The chest physician now also finds himself required to be well schooled in physiology. The understanding of respiratory gas exchange and other aspects of pulmonary function is paramount for his survival, and for that of his patients. Indeed, many chest specialists must guard against becoming so imbued with gadgetry in the pulmonary function laboratories, that they lose interest in the patient. This is not intended to decry research in the basic scientific aspects of pulmonary function and in animal experimentation. What I do mean to emphasize is that the clinical chest specialist must still regard very highly what the patient tells him, and not tend to discount the patient's testimony because of a certain figure that he may see on the pulmonary function laboratory report.

One phase of medicine that the decline of tuberculosis has not affected in the role of the chest physician has been his intense interest in radiology, as illustrated so well by Dr. H. Corwin Hinshaw, Sr. Indeed, some of the best chest roentgenologists have been the old time phthisiologists. Many times recently, it has been amusing at conferences to observe a learned discussion of a chest roentgenogram by various types of physicians and note that the newer chest physician may fail to mention the possibility of tuberculosis causing the particular chest x-ray shadow in question. However, in addition to maintaining interest in bronchography and planigraphy, the present day chest specialist must also be more than passingly familiar with various types of lung scanning techniques employing radioactive materials and with various intravascular contrast studies. There has been increasing interest in various arterial venous malformations. The chest specialist many times may also become adept at passing cardiac catheters and measuring various pressure gradients and oxygen saturations in trying to delineate just what happens in bronchopulmonary diseases. There has also been something new on the horizon in bronchography with the beautiful work of Dr. Jay Nadel and associates with tantalum as a contrast medium.

The reader has perhaps noticed by now that I have failed to mention, amongst all the various types of practitioners, the surgeons and, more especially, the thoracic surgeon. They

are among my dearest friends and have helped me out of many a difficult diagnostic and therapeutic situation. The chest physician is able to derive much more benefit now from his surgical colleagues by being better able to assess operative and anesthetic risk and to aid in the postoperative care in Intensive Care Units or Respiratory Care Units. I think that one of the great benefits from modern medicine has been the doing away with the artificial barriers that have long existed between internists and surgeons, and to make the internist and surgeon real colleagues interested in the total care of the patient rather than the old fashioned concept of considering the two groups as competitors and considering surgery as a "last resort in a moribund patient".

The present day chest physician, by being more gregarious, finds himself called upon much more to participate in the education of various other groups. He frequently must give talks to community groups at Grade School, High School, College and Scout levels on such things as smoking, other forms of air pollution, industrial hazards and the like. In addition, in the medical society or hospital setting, the chest physician must participate extensively in the teaching of intensive care techniques, particularly of a respiratory nature but also embracing all aspects of fluid and electrolyte balance, cardiac care, intubation and monitoring of vital signs and resuscitation techniques, to colleagues, nursing staffs and allied paramedical personnel. I personally have found this to be necessary and also enjoyable, not only in the setting of the large hospital such as Letterman General Hospital but also in the setting of Ridgecrest Community Hospital, located in the town of Ridgecrest in the Mojave Desert. Inhalation therapy service can be and should be available not only in the 1,000 bed university hospital or the 550 bed Army general hospital but also in the 76 bed community hospital such as we have here in Ridgecrest.

I have attempted, in somewhat of a philosophical vein it is true, to illustrate the changes in the attitude and in the day-to-day work of the chest physician that have been occasioned by the decline of tuberculosis. The chest physician finds himself involved now in all phases of medicine and therefore finds himself actually to be more of a generalist

than he was a pure phthisiologist. I must add one word of caution in closing, however. Now that we as chest physicians have become so adept at so many things, we still must not lose sight of the fact that tuberculosis still exists and still requires detection and care. Careful contact work and careful screening must be done under our supervision. Tuberculosis must still be considered in the differential diagnosis of obscure clinical cases and in patients with so-called fevers of undetermined origin. The chest physician who forgets about tuberculosis, even with all the other improvements in his total outlook, can never be considered as good a doctor as the chest physician who remembers this ancient plague.

"SHOCK LUNG"

John F. Murray, M.D.*

"Shock lung" is a syndrome characterized by progressive, clinical, radiographic, and physiological alterations in lung function that follow an episode of severe hypotension. This syndrome has been observed following hypotension from many causes; trauma, hemorrhage, burns and gram-negative sepsis. Although pulmonary manifestations may appear during the acute hemodynamic crisis, more commonly there is a latent period of 12-24 hours during which respiratory abnormalities are minimal or nonexistent. After the latent period, the patient begins to complain of shortness of breath that increases in severity. If arterial blood gases are being monitored during this interval, a progressive fall of arterial oxygen tension can be documented. Patients who are receiving intermittent positive pressure ventilation will require increasing inspiratory pressures to maintain satisfactory alveolar ventilation because the lung becomes stiff (less compliant). This same phenomenon in patients who are being ventilated with a volume respirator will cause a rise in inspiratory pressure. Serial chest roentgenograms will show patchy, irregular, pulmonary infiltrations that rapidly increase in extent as the disorder worsens. Although the mortality rate is difficult to document, owing to confusion in defining the presence of "shock lung", a high percentage (70-80 percent) of deaths following severe hypotensive episodes are caused by progressive respiratory insufficiency.

The pathological findings that have been described in "shock lung" are uniform. The gross lung specimen is intensely hemorrhagic, congested and airless; the solid, red appearance of the cut surface is nearly always described as resembling liver. In microscopical sections, one sees intense vascular congestion with extravasated fluid and blood in the interstitial

*Professor of Medicine, University of California, San Francisco, Chief, Chest Service, San Francisco General Hospital, and Civilian Consultant, Letterman General Hospital

and alveolar spaces. Hyaline membranes lining alveoli and small airways, and platelet-fibrin aggregates (microemboli) in small blood vessels are frequently found.

Etiology

A number of factors operating either alone or in concert are thought to contribute to the development of "shock lung". These can be divided into intrinsic and extrinsic factors as shown in TABLE I.

TABLE I

FACTORS CONTRIBUTING TO "SHOCK LUNG"

INTRINSIC	EXTRINSIC
Toxins	Infection
Microemboli	Overhydration
Myocardial failure	Oxygen, drugs, etc.

Intrinsic factors are those that are directly related to the cause of the hypotensive episode per se; they include toxins (endotoxins, ingested poisons, inhaled gases), microemboli (fat, platelet-fibrin aggregates), myocardial failure (myocardial infarction, barbiturate overdose) and release of vasoactive substances (catecholamines, histamine, bradykinin, fibrinopeptides).

Extrinsic factors are those that are not essential components of the shock state but are externally introduced, often during attempts at therapy by the attending physician. Extrinsic factors include pulmonary infection, overhydration, and the toxic effects of oxygen and other drugs.

Pathophysiology

Among the earliest physiological derangements in "shock lung" is the development of arterial hypoxemia (low arterial Po_2). The hypoxia worsens as the syndrome progresses and serves as a useful guide to its severity and prognosis. Hypoxemia occurs largely on the basis of right-to-left

shunting of blood through the lung; the shunt pathways presumably occur through alveoli that have collapsed, owing to instability, or are filled with either blood, pus, or edema fluid. As alveoli collapse, the lung becomes "stiffer", and requires greater ventilator pressure to achieve a given tidal volume. Conversely, if the patient is on a constant-volume respirator, it will be noted that inspiratory pressure rises progressively.

Under normal conditions, one-fourth to one-third of each breath is "wasted" in the sense that it does not contribute to oxygen uptake or carbon dioxide elimination. (Others have called this fraction "physiological dead space".) Most of the normal wasted ventilation is in airways from the trachea down to the terminal bronchiole. In "shock lung", however, wasted ventilation may rise considerably, so that half or even three-quarters of each breath does not go to alveoli where it can contribute to gas exchange. In order to maintain normal carbon dioxide elimination, therefore, patients with large increases in wasted ventilation must increase their minute ventilations considerably to make up for the amount that is wasted. In the early stages of the evolution of "shock lung", arterial P_{CO_2} is normal or even slightly low, but as the mechanical properties of the lung become more severely impaired and wasted ventilation increases, finally P_{CO_2} increases and is an ominous prognostic sign.

TREATMENT

The essential elements of treatment are listed in TABLE II. Since the presence and severity of "shock lung" depend in part on the duration and extent of the initial hypotensive episode, every effort should be made to direct specific treatment towards the underlying condition as early and as vigorously as possible. Therapy may consist of volume replacement with blood, plasma or plasma substitutes, the administration of vasoactive drugs and in cases with gram-negative sepsis the administration of antibiotics and possibly large doses of adrenal cortical steroids.

Early ventilatory support is essential, both to maintain adequate arterial blood gas tensions as well as to prevent unstable alveoli from collapsing and causing hypoxia and

reducing compliance. The patient should be ventilated at an adequate tidal volume (12-15 ml/kg) and sighed every 10-15 minutes. If hypoxia develops and progresses despite these precautions, the use of continuous end expiratory pressure at levels of 5 or 10 cm H_2O pressure is advisable.

TABLE II

TREATMENT OF "SHOCK LUNG"

- ⇒ Specific treatment underlying condition
  - Volume replacement
  - Vasoactive drugs
  - Antibiotics
- ⇒ Supplementary oxygen (maintain arterial oxygen tension between 80 to 100 mg Hg)
- ⇒ Ventilatory Support
  - Maintain carbon dioxide tension between 40 to 45 mm Hg
  - Deep breath every 10 to 15 minutes
- ⇒ Diuretics
- ⇒ ? Heparin

If the patient has been overhydrated or if there is evidence of redistribution of intravascular or interstitial fluid into the thorax, diuretics are indicated. The administration of heparin is controversial. Some favor its use almost routinely on the basis that disseminated intravascular coagulation is a frequent accompaniment of virtually all shock states. On the contrary, in view of hazards of heparin administration in individuals with hemorrhagic conditions or multiple traumatic injuries, many (this author included) recommend withholding the drug unless there is definite laboratory evidence of the presence of intravascular coagulation.

If oxygen is administered, it should be given only in amounts sufficient to raise the patient's arterial P_{O_2} to

between 80 and 100 mm Hg. If right-to-left shunting is particularly severe and would require prolonged use of high inspiratory concentrations of oxygen (greater than 70 percent), one should be satisfied with an arterial P_{O_2} of only 50-60 mm Hg because this is adequate to oxygenate about 85-90 percent of the available hemoglobin.

SUMMARY

Respiratory failure is a frequent and important accompaniment of shock and occurs following shock of many different causes. The clinical constellation constitutes a syndrome to which multiple factors undoubtedly contribute.

The major physiological abnormalities are: (1) a pronounced reduction in arterial oxygen tension from a large right-to-left shunt, (2) a striking increase in the patient's wasted ventilation, and (3) a pronounced alteration of mechanical properties that affect the patient's ability to breathe spontaneously or to be ventilated.

Adequate treatment requires an understanding of the pathophysiological disturbances that take place in shock. Attention should be directed toward preventing some of the complications that may arise through injudicious therapy. Early assisted ventilation and maintenance of the patient's arterial blood gas tensions may prevent the evolution of the lung lesions associated with this condition.

If there was nothing wrong in the world

there wouldn't be anything for us to do.

—George Bernard Shaw

CHRONIC OBSTRUCTIVE PULMONARY DISEASE
The Present Challenge

LTC Edward E. Mays, MC

Chronic bronchitis and emphysema now constitute the most important chronic lung diseases in this country. Deaths from these two diseases have approximately doubled every five years since 1950./1/ Emphysema ranks second only to heart disease as the most frequent diagnosis among workers becoming eligible for disability pensions. Surveys from various areas indicate that up to 25 percent of all persons over age 40, or about 14 million Americans, have detectable chronic obstructive pulmonary disease (COPD). Mitchell and associates /2/, via autopsy studies in males over age 40, found that only 50-60 percent of patients with COPD contributing to death are recorded as having clinical disease during life. In another autopsy study of unselected males, Boushy and co-workers /3/ compared their results with those of four similar studies and concluded that approximately 65 percent of fume-fixed lungs showed morphologic emphysema, predominantly centrilobular in type. Both studies indicate that the true incidence of COPD in our population is seriously underreported.

Knowledge of the etiology and pathogenesis of COPD is incomplete, precise medical research and communication having been hampered for many years by the lack of clear definitions of the subgroups in the disorder. Over the past several years, workable definitions have become generally accepted /4/, however, there remain inherent contradictions and vagaries. Strict adherence to these definitions, particularly in the early clinical and laboratory situations, tends to obscure early diagnoses and to restrict the development of unifying etiological concepts. For example, chronic bronchitis is defined and classified on the basis of symptomatology, e.g. cough with mucus production is a key symptom. Provincial definitions, however, require various durations of sputum production. Patients are often unaware of or deny the symptom, and incredibly, the pathological sine qua non,

mucous gland hyperplasia, is absent at autopsy in nearly half the clinically diagnosed cases./5/ Moreover, when mucous gland hypertrophy is present, it is more clearly related to cigarette smoking habits than to bacterial or viral infection /6/, factors which remain etiologically uncertain. Further, bronchorrhea occurs in other conditions, including asthma and cystic fibrosis, even when mucous gland hypertrophy is absent./7/

Similarly, the definition of emphysema depends completely upon pathological criteria, about which there is much confusion if the lungs are not inflated and fixed before evidence is sought. The development of criteria for the clinical diagnosis of emphysema has been considerably retarded by adherence to this dictum, and some experts even proclaim that emphysema cannot be diagnosed clinically. In fact, emphysema of the panlobar type can often be diagnosed from evidence derived by clinical, radiographic, and pulmonary function studies.

In addition, the picture is almost always muddled by the tendency of chronic bronchitis, emphysema, and even asthma to coexist, making it impossible to assess by conventional evaluation the relative contribution each disease makes to the over-all disability of a subject./8/ It is agreed that airway obstruction and derangement of the distribution of ventilation to the pulmonary capillary bed are the prime incapacitating features of each disease.

Significant attempts have been made in clinically differentiating chronic bronchitis from emphysema. Briscoe and Nash /9/ in 1965, based upon 10 clinical criteria, suggested that the two disease types might be divided into Type A (emphysema) and Type B (bronchitis). Other workers have made comparable distinctions with varying degrees of success. As a result, clinicians may now classify patients as having "predominantly" emphysema or bronchitis, rather than as having pure syndromes of either, with a spectrum of intermediate overlapping. The clinical presentation may be complicated by the coexistence of bronchospasm, bronchiectasis, bronchiolitis, pulmonary fibrosis, or other disorders.

The etiology of neither emphysema nor chronic bronchitis is clearly known. Present evidence indicates that certain constituents of cigarette smoke and of urban air pollutants are important etiological factors in both. Lower airway

infections cause worsening of both forms of disease. These and similar links, and the observation that the two diseases coexist in most individuals suggest a shared pathogenic relationship.

A significant discovery and subsequent follow throughs, initially by Eriksson and workers /10,11/ in 1965 have led to a remarkable stimulus in thinking and research on the etiology of emphysema. Subsequent investigations by many others have led to the conclusion that a small percentage of subjects having emphysema are afflicted by an hereditary deficiency of alpha$_1$-antitrypsin (AAT), the main proteinase inhibitor in normal human serum. This shortage of antitryptic activity in the lungs leaves such an individual vulnerable to the proteolytic enzyme, trypsin, released from dying or from actively phagocytosing leukocytes and alveolar macrophages. Recent work tends to pinpoint elastin, the fabric that enhances lung recoil, as the trypsin substrate. Absence of AAT may also potentiate recurring lung infections, since it has been shown to have some antibiotic activity. Some gram-negative bacteria inactivate AAT, however, and may play a role in depleting the local infected area of antitryptic activity.

Homozygous AAT-deficient patients are subject to developing clinical emphysema at an earlier age and to include a higher percentage of females than other COPD patients. Thirty percent of these patients have peptic ulcer histories or active disease, a considerably higher ratio than in the normal population. The emphysematous changes occur predominantly in the lower lung fields, the areas of greatest circulation.

The majority of emphysema patients, who are not AAT-deficient, suffer from a still unknown defect, and may theoretically develop the disease by a mechanism similar to that described. In this connection, alveolar macrophages have been shown to yield two enzymes which show appreciable activity against elastin. Another clue toward the further understanding of enzymatic digestion in the lung is the fact that phagocytes release fewer lysosomal enzymes during their digestive processes if their intracellular cyclic AMP level is increased by stimulation with prostoglandin E$_1$.

As an aside, two other congenital conditions are known to be associated with deficiencies of circulating AAT. Newborns with the respiratory distress syndrome and AAT deficiency may survive if they are able to elevate serum enzyme inhibitor levels during the first two days of life; others tend to die. In the other childhood AAT-deficient disease, familial childhood cirrhosis, hepatic cellular dysfunction prevents already synthesized AAT from entering the circulation.

As for significant leads toward the etiology of chronic bronchitis, cigarette smoking is the only well-established etiology. However, certain constituents found in environmental air pollution are suspect if not clearly proven to be associated with chronic airway disease./12,13/ Acute changes in airway resistance and in the incidence of respiratory symptoms associated with high levels of various pollutants have been clearly demonstrated. The effects of low levels of exposure over prolonged time intervals is much less clear.

As suggested by the above cited autopsy studies which detailed the true incidence of emphysema, the diagnosis of COPD is not always simple. Granted that the typical case of well-established COPD presents to the clinician with dyspnea or productive cough, or both. Early cases, who theoretically could obtain effective preventive measures before significant irreversible lung or airway changes occur, may have few recognizable symptoms or signs. Cough may be disguised as merely throat-clearing or proclaimed a "smoker's cough" of little significance. Dyspnea may be avoided by subconscious reductions in activity, or accorded to aging.

The commonly utilized physical signs, recently reviewed by Campbell /14/, are those of well-established disease, related to large airways obstruction and to over-distension of the chest. There is also considerable observer variability in the detection of physical signs /15/, even in well-established disease, among experienced observers. With specific training, the frequency of recognition of certain clinical signs improves somewhat, but observer variability remains. These observations are even more important when one considers that a significant number of medical training programs, even of the university type, have no formal chest training. The effects may be seen among our interns each year.

In a further attempt at unraveling the thorny problem of establishing pathophysiological differences between emphysematous and bronchitic types of COPD, Filley, et al /16/ published the results of an impressive study. Again, basing classifications on the presence or absence of certain well-established clinical criteria such as weight loss, cardiac enlargement, congestive heart failure, and hematocrit greater than 60 percent, they have buttressed the argument for separation of COPD patients into "pink puffers" (emphysema), and "blue bloaters" (chronic bronchitis). Although their conclusions appear to be relevant to understanding the course and prognosis of COPD, that the most consistent differences are in pulmonary oxygen transport and tissue oxygenation, it is readily apparent that the entire study refers again to far-advanced disease. Bates /17/ has recently seriously questioned the benefits to be derived from splitting COPD into these two groupings, arguing that the separations are artificial and that they retard progressive thinking on pathogenesis. Such an argument may have merit, but appears to be quite shallow in view of the stimuli to research that we have noted during this recent "splitting" era. It becomes a difficult task to ignore clear morphological and pathophysiological differences.

Further difficulty in diagnosis resides in observations that patients with COPD may present to the clinician with a wide variability of clinical and physiological findings. Burrows, et al /18/, in a study of 175 outpatients with definite COPD, found that they often do not present with characteristic symptoms and signs. While less than one percent denied all dyspnea, this symptom is unfortunately nonspecific and is seen in a variety of disorders. Wheezing was denied in 23 percent of cases, sputum production in 14 percent, and cough in 11 percent. As for physical signs, decreased vesicular breath sounds were noted in only 46 percent, rhonchi in 35 percent, and central cyanosis or clubbing in only four percent each. Laboratory findings were no more helpful, as 36 percent had normal arterial O_2 saturation, 77 percent had normal arterial CO_2 tensions, and only 14 percent had definite chest roentgenographic evidence of emphysema (34 percent had entirely normal chest roentgenograms). Standard pulmonary function test parameters correlated poorly with symptoms, signs, and with other laboratory tests.

Hence, if one is alert for only classic emphysematous or bronchitic types of COPD, the diagnosis may frequently be missed in mild or even in advanced disease./19,20/ Another reason for this tendency is that detectable symptoms and signs of COPD are often overshadowed by extrapulmonary manifestations and by complications. As a result, patients may present themselves to a number of specialists other than chest physicians. TABLE I.

Recent research suggests that the pathophysiology and even the morphology in COPD may be more similar than previously supposed. Patients with early symptoms or other evidence of chronic bronchitis, emphysema or bronchiectasis may have normal routine pulmonary function testing, but significant abnormalities of ventilation-perfusion ratios within the lungs./21,22/ Such a change tends to promote hypoxemia, and is attributable to obstruction in small peripheral airways. It appears that the major site of airflow resistance in any type of COPD is in the small airways (bronchioles), and can occur without morphologic evidence of other lung disease, or cigarette smoking. This obstruction is the result of mucus plugging, inflammation, and distortion of bronchiolar walls, without necessarily having an associated abnormality of parenchymal elastic recoil (the latter known to be important in the air-trapping of later stages of COPD). Similar changes occur in early AAT deficiency, however, pulmonary capillary loss may be an even earlier stage./23/ D.V. Bates /8/ has given a comprehensive review and presented a theoretical unifying concept towards the etiology and natural history of these disorders.

Advances in treatment appear to all to be directed toward the later stages of COPD, i.e., respiratory failure. Therapeutic indications and measures are embodied in the reports which emphasize oxygen therapy by the Denver group of investigators./24/ Perhaps, in view of the above related effects of prostoglandin on lysosomal activity, we may be on the verge of therapy directed at the cellular level, and conceivably prevent the nonreversible destructive changes with which we have become so familiar in COPD.

TABLE I

SOME MEDICAL SPECIALISTS TO WHOM COPD* PATIENTS MAY PRESENT

CARDIOLOGIST - Dyspnea, CHF, arrhythmias, cyanosis

NEUROLOGIST - Respiratory encephalopathy

GASTROENTEROLOGIST - Gastrointestinal bleeding, abdominal pain, nausea and vomiting, asterixis

ENDOCRINOLOGIST - "Myxedema"

ALLERGIST - "Asthma"

HEMATOLOGIST - Polycythemia, fatigue and weight loss

NEPHROLOGIST - Acid base balance, renal failure

PSYCHIATRIST - Difficult cerebration, "neuroses"

THORACIC SURGEON - Pneumothorax, large bullae, lung cancer

TUBERCULOLOGIST - "Cavities"

RHEUMATOLOGIST - Clubbing, hypertrophic osteoarthropathy

GENERAL SURGEON AND ANESTHESIOLOGIST - Postoperative respiratory failure

OTOLARYNGOLOGIST - Sinusitis

ONCOLOGIST - Weight loss, lung cancer

*Chronic obstructive pulmonary disease

In summary, I have reviewed some of the most recently obtainable information regarding the tremendous and growing importance of COPD. It seems fitting to quote Mitchell /25/ at this point.

> In spite of numerous recent advances in our knowledge of this subject, we need to know much more about the pathogenesis of chronic airways obstruction. However, even with our present knowledge, physicians can do a great deal to reduce the speed of deterioration and possibly even prevent disabling chronic airways obstruction. This requires a very careful look at patients who consult their physicians for other reasons ..... Prevention is always better than treatment, and in virtually no other field of medicine does preventive management (from cigarette smoking hazards, and by bronchial hygiene and by prevention or early treatment of deep respiratory infections) give more promise of widespread benefit.

References

1. Report of the Task Force on Chronic Bronchitis and Emphysema. Bulletin National Tuberculosis Association, Vol 53, No 5, 1967
2. Mitchell RS, Walker SH, Silvers GW, et al: Frequency and severity of anatomic emphysema in men over 40 dying in two Denver hospitals. Arch Environ Health 18:667, 1969
3. Boushy SF, Greenber SD, Jenkins DE, et al: The prevalence of emphysema in 67 unselected male autopsies. Dis Chest 53:497, 1968

4. American Thoracic Society. Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. Statement by Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases. Amer Rev Resp Dis 85:762, 1962
5. Mitchell RS, Ryan SF, Petty TL, et al: Significance of morphologic chronic hyperplastic bronchitis. Amer Rev Resp Dis 93:720, 1966
6. Field WEH, Dave EN, Reid L, et al: Bronchial mucous gland hypertrophy; its relation to symptoms and environment. Brit J Dis Chest 60:66, 1966
7. Liebow AA, Smith DE: Bronchial mucus production in health and disease. In The Lung. Baltimore: Williams & Wilkins Co., 1968. Chapter 8
8. Bates DV: Chronic bronchitis and emphysema. Medical Progress. New Eng J Med 278:546 and 600, 1968
9. Briscoe WA, Nash ES: Slow space in chronic obstructive pulmonary disease. Ann N.Y. Acad Sci 121:706, 1965
10. Laurel CB, Eriksson S: Electrophoretic a1-globulin pattern of serum a1-antitrypsin deficiency. J Clin Lab Invest 15:132, 1963
11. Eriksson S: Studies in a1-antitrypsin deficiency. Acta Med 177 (Supp. 432):1, 1965
12. Air Pollution and Health. A statement by the ATS Committee on Air Pollution. Amer Rev Resp Dis 93:302, 1966
13. Ehrlich R: Effect of air pollutants on respiratory infection. Arch Environ Health 6:638, 1963
14. Campbell EJM: Physical signs of diffuse airways Obstruction and lung distension. Thorax 24:1, 1969
15. Godfrey S, Edwards RHT, Campbell EJM, et al: Repeatability of physical signs in airways obstruction. Thorax 24:4, 1969
16. Filley GF, Beckwitt HJ, Reeves JT, et al: Chronic obstructive bronchopulmonary disease. I. Oxygen transport in two clinical types. Amer J Med 44:26, 1968
17. Bates DH: Lecture presented at University of Colorado School of Medicine, 1 April 1971
18. Burrows B, Niden AH, Barclay WR, et al: Chronic obstructive lung disease. I. Clinical and physiologic findings in 175 patients and their relationship to age and sex. Amer Rev Resp Dis 91:521, 1965
19. Cohen BM: When to suspect that masquerading malady: Obstructive lung disease. Consultant, Feb 1967, p 32

20. Anderson AE, Jr: Pitfalls in diagnosing emphysema. Consultant, Feb 1967, p 39
21. Anthonisen NR, Bass H, Oriol A, et al: Regional lung function in patients with chronic bronchitis. Clin Sci 35:495, 1968
22. Macklem PT, Thurlbeck WM, Fraser RG: Chronic obstructive disease of small airways. Ann Intern Med 74:167, 1971
23. Levine BW, Talamo RC, Shannon DC, et al: Alteration in distribution in pulmonary blood flow. An early manifestation of AAT deficiency. Ann Intern Med 73:397, 1970
24. Petty TL, Nett LM, Finigan MM, et al: A comprehensive care program for chronic airway obstruction. Methods and preliminary evaluation of symptomatic and functional improvement. Ann Intern Med 70:1109, 1969
25. Mitchell RS: Outlook in emphysema and chronic bronchitis. Editorial. New Eng J Med 280:445, 1969

CONTROL OF VENTILATION IN RESPIRATORY FAILURE

MAJ Allen S. Lipschultz, MC

Respiratory failure, arbitrarily defined as an arterial carbon dioxide tension greater than fifty, or arterial oxygen tension less than fifty /1/, is a frequently recognized complication of a number of disease states./2-4/ The treatment of this condition commonly involves ventilatory support using pressure or volume cycled respirators in an intensive care setting. With increasing use of these respirators associated complications have appeared./5/ Many of these complications are preventable by understanding the pathophysiological events that occur in these patients and employing physiological principles in their management.

The decision to ventilate the patient artificially may be immediately obvious (e.g. cardiac arrest), or require a careful assessment of the patient's previous history, determination of changing physical findings and analyses of arterial blood gases and other laboratory findings (e.g. for patients with chronic obstructive lung disease and progressive carbon dioxide retention or viral pneumonia and decreasing arterial oxygen tension). Frequently the decision is made on the basis of a projected analysis of the patient's course. Detailed discussions of this decision-making process have been adequately reviewed elsewhere./6-9/

Once mechanical ventilation is desired, control of the airway is necessary and an endotracheal tube should first be inserted in the airway. Subsequently the decision to perform a tracheostomy can be made./5/

Mechanical ventilation may be achieved with a volume or pressure-cycled ventilator./10-13/ When high inspiratory pressures, or end expiratory resistance at fixed tidal volumes is desired, volume ventilators may be more suitable./14-16/ The subsequent depression of cardiac output, occurrence of pneumothorax or fluid retention may occur with either type of ventilator, but probably is more common with volume-cycled

machines./5,8,17/ The various types of ventilators are adequately reviewed in the text of Young and Crocker./11/

THE CONTROL OF ARTERIAL CARBON DIOXIDE TENSION ($PaCO_2$) AND pH

When the physician has established the airway for the patient and has a ventilator chosen, he must then decide on an appropriate level of alveolar ventilation which will correct the arterial blood gas and acid-base disturbance. This presents a particular problem because patients in respiratory failure usually have underlying chest wall or pulmonary disease./18,19/ These patients have been shown to have abnormal ventilatory requirements./19/ The abnormality is primarily due to an increase in the physiologic dead space (i.e. that amount of inspired air which does not come into contact with pulmonary blood flow). In addition, alterations in carbon dioxide production may be important.

Measurement of minute ventilation, then, can be misleading if some idea of the wasted ventilation is not known. For this reason the Radford nomogram /20,21/ (a nomogram for predicting basal ventilation from body weight, sex and breathing frequency) is impractical because it applies only to normal lungs. Other nomograms incorporating the actual measurement of wasted ventilation, and therefore allowing for a more precise control of ventilation, are impractical for many intensive care units today./22/ Because of the need to rapidly determine an appropriate minute ventilation, a nomogram has been developed relating minute ventilation to arterial carbon dioxide tension. Figure 1. The legend explains the method./23/ Both measurements are readily obtainable in intensive care units. The minute ventilation may be measured with a Wright respirometer or similar measuring device. The arterial carbon dioxide tension is determined using the electrode technique./24/ The VD/VT line is the isopleth that coincides with the minute ventilation ($\dot{V}E$) - $PaCO_2$ point. Although the nomogram is subject to error when the patient's carbon dioxide production fluctuates, it has been proven to be reliable in predicting changes in $PaCO_2$ when the minute ventilation and VD/VT points are known./23/

The initial minute ventilation set by the physician to achieve a desirable $PaCO_2$ tension is somewhat arbitrary because the VE-$PaCO_2$ point is not known. Seven to ten liters minute ventilation, depending on the patient's size, underlying disease and arterial pH is accepted by most authorities as an effective starting point./8,11/ It is of utmost importance to obtain an arterial blood gas measurement and simultaneously measure minute ventilation approximately 30 minutes later. This enables one to decide more accurately on an appropriate minute ventilation because the VE-$PaCO_2$ point will be established and the patient should then follow a given VD/VT line.

Careful control of ventilation is critical. Inappropriate ventilatory control usually results from physician's errors in judgement of minute ventilation required to achieve a given $PaCO_2$ tension. Rapid correction of the respiratory acidosis with resulting metabolic alkalosis can result in decreased central blood flow /25/, shift of the oxyhemoglobin dissociation curve to the left, resulting in decreased tissue oxygenation /26/, seizures, hypotention, apnea /5,27,28/, cardiac arrhythmias refractory to therapy /29/ and heart failure.

Alternatively, some patients may be hypoventilated with exacerbation of the respiratory acidosis./12,13/ This particular problem tends to occur when the patient is "out of phase" with the ventilator. In some instances sedatives may have to be administered and, rarely, muscular paralyzing agents are required to achieve ventilator-patient coordination.

Occasionally chloride deficiency may exist secondary to a variety of causes./30/ This will result in a coexistent metabolic alkalosis and further complicate ventilatory management. Alternatively, reductions in cardiac output, renal failure, or severe hypoxemia may result in a superimposed metabolic acidosis and necessitate bicarbonate therapy./31-34/

When adequate ventilator support is achieved, frequent measurements of arterial $PaCO_2$ and minute ventilation are still necessary. Changes in the patient's pulmonary condition may lead to wide fluctuations in arterial $PaCO_2$ tension for reasons already discussed. Flow sheets are particularly desirable to enable the physician to follow the many variables measured.

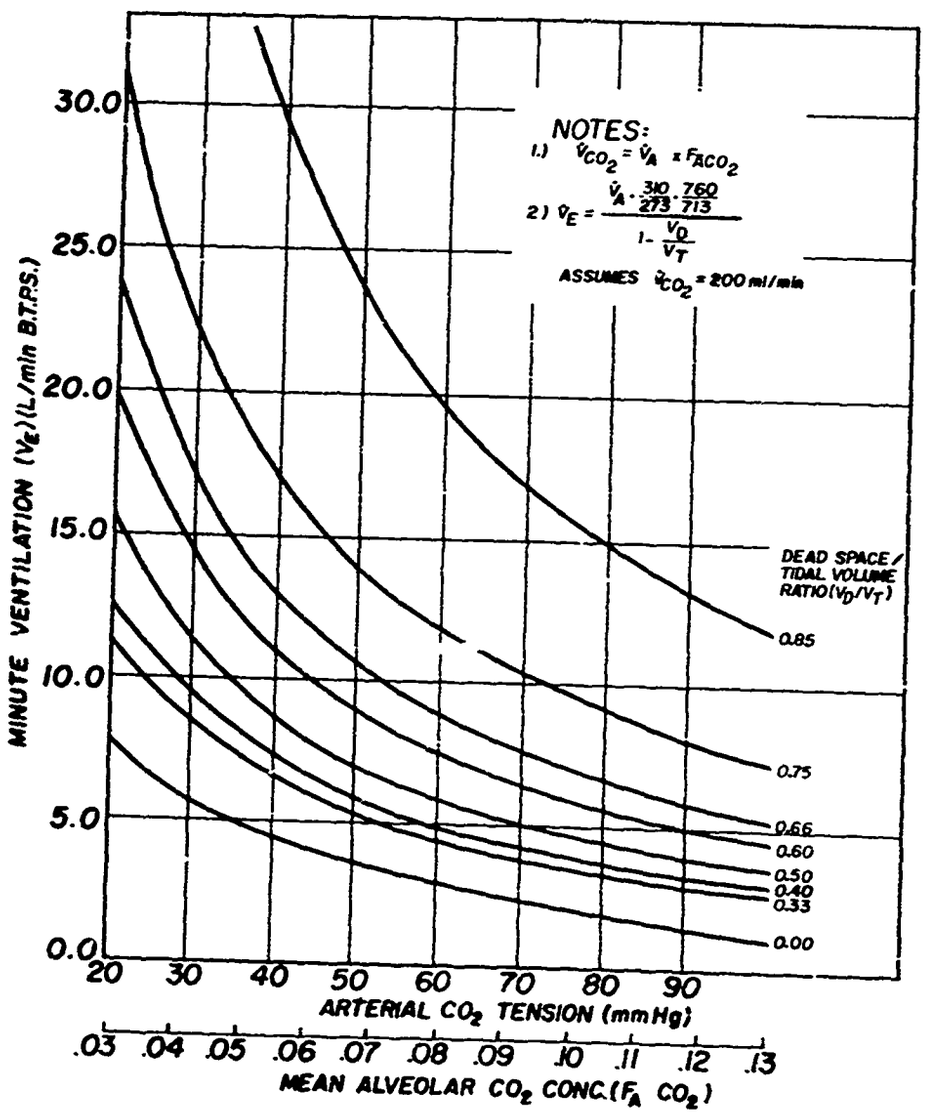

Fig. 1. Graph: Minute ventilation-arterial CO_2-VD/VT

THE CONTROL OF MECHANICAL VENTILATION
Minute Ventilation - Arterial CO_2 - VD/VT Graph (Figure 1)

1. Patient is placed on a respirator. An average minute ventilation is achieved (7-10 L/min), and measured with a Wright respirometer.
2. Following ½ hour on the respirator an arterial blood sample is obtained and analyzed for arterial CO_2 tension. ($PaCO_2$) Simultaneously the minute ventilation is measured.
3. The minute ventilation and corresponding arterial CO_2 ($PaCO_2$) are plotted on the graph. The VD/VT ratio is obtained from noting the isopleth that coincides with this point.
4. To obtain the required minute ventilation to achieve any desired $PaCO_2$, a vertical line is drawn from the $PaCO_2$ value on the horizontal axis to the VD/VT isopleth obtained in step 3. From this point a horizontal line is drawn perpendicular to the vertical axis to obtain the required minute ventilation.
5. The respirator is then adjusted. The calculated minute ventilation (Tidal Volume X Rate = Minute Ventilation).
6. As the patient's lung problem improves, the VD/VT ratio will hopefully be reduced requiring less minute ventilation. The respirator should be reset to achieve this new minute ventilation. Worsening of the pulmonary problem will require opposite adjustments of the ventilator.
7. The patient's course must be monitored with arterial blood gases as indicated. Whenever an arterial sample is drawn, the minute ventilation should be noted and recorded and a new VD/VT value obtained.
8. Use the new VD/VT ratio for determining the patient's new minute ventilation.

The effective compliance of the lung and chest wall is an important measurement that should be followed and is readily determined./8,19/ This relates tidal volume to peak airway pressure. It is measured by dividing the tidal volume by the peak airway pressure observed on the ventilator. Normal effective compliance is 35-45 ml/cmH_2O. Improvement in the pulmonary status frequently is noted by improvement in effective compliance. In fact, this may be a more sensitive measurement of improvement than the VD/VT, arterial $PaCO_2$, or chest roentgenogram.

THE CONTROL OF ARTERIAL OXYGEN CONTENT

All newer volume ventilators allow for variable inspired oxygen concentrations. Veriflow oxygen devices may be attached

to Bird respirators to give them the same flexibility. Other pressure cycled machines (Bennett) should be run on compressed air with oxygen bubbled through the nebulizer to allow for variable oxygen flow rates. In all cases periodic measurement of the inspired oxygen concentration is desirable. This is accomplished simply with a portable oxygen analyzer./11/

While the control of inspired oxygen is important, the ultimate aim is to achieve an arterial oxygen tension consistent with adequate tissue oxygenation. Direct measurement of tissue oxygen content is not available at the present time. One now must rely on the arterial oxygen tension and the shape of the oxyhemoglobin dissociation curve to estimate the oxygen content (hemoglobin oxygen + dissolved oxygen) of circulating blood./35/ A knowledge of cardiac output allows for a more precise estimation of the tissue oxygen levels. In many situations one can assume a normal cardiac output, however, with coexistent cardiac disease, hypovolemia, or positive end-expiratory pressure, these assumptions may be misleading. /32,36-38/ In addition, severe anemia will also reduce total oxygen content despite a normal oxygen tension and a cardiac output./35/

The shape of the oxyhemoglobin dissociation curve is known, and variations in its shape with changes in pH and temperature can be predicted./35/ Rough estimates of cardiac output can be made at the bedside and in most cases this will be satisfactory. In most situations, then, measurement of the arterial oxygen tension is all that is necessary.

At an arterial PaO_2 of 60 mm Hg the blood is 90 percent saturated, depending on arterial pH. This gives a more than satisfactory oxygen content. At arterial oxygen tensions below 50 mm Hg the oxyhemoglobin dissociation curve becomes steep and small changes in arterial oxygen tension allow for large changes in arterial oxygen content./35/ If one could be certain that the arterial PaO_2 would stay between 50 and 60 mm Hg throughout the patient's course on the ventilator this would probably be satisfactory. Unfortunately, changes in position of the patient, endotracheal suctioning, pooling of secretions, and so forth, tend to lower the arterial oxygen tension. For this reason, a margin of safety is desirable. In most cases, keeping the arterial oxygen tension at

approximately 80 mm Hg gives a comfortable margin of safety without excessive inspiratory oxygen concentrations, although lower levels may be acceptable when oxygen toxicity becomes a problem.

THE PROBLEM OF OXYGEN TOXICITY

Some patients have major ventilation-perfusion imbalance resulting in large alveolar-arterial oxygen tension differences. This is commonly seen in adult respiratory distress syndrome (RDS), and "shock lung"./14,15/ In these patients inspired oxygen concentrations as high as 100 percent may be necessary to keep the arterial PaO_2 at a level above 50 mm Hg. While one should not compromise this level, the problem of pulmonary oxygen toxicity becomes apparent when inspired oxygen concentrations near 100 percent are used for prolonged periods of time (periods in excess of 24 hours)./41-45

Pulmonary lesions have been reported retrospectively by many groups evaluating the effects of oxygen therapy at high concentrations for days./43-45/ Postmortem studies on some of these patients have shown pulmonary capillary congestion, replication of endothelial cells, accumulation of interstitial and alveolar fluid, intra-alveolar hemorrhages and hyaline membrane formation. Prospective studies on the effects of 100 percent oxygen at one atmosphere of pressure suggest that after 30 hours of treatment physiologic changes can be seen, however, pathologic changes are nonspecific./42/ Shorter periods (24 hours or less) appear to be safer./41,44/ In these studies there were not large alveolar-arterial oxygen ($A\text{-}aDO_2$) tension differences initially.

The effects of 100 percent oxygen on the diseased lung where large $A\text{-}aDO_2$ differences exist are controversial. Studies on the effects of venous admixture on the development of pulmonary oxygen toxicity have been done in experimental animals./46,47/ These two reports resulted in opposite conclusions.

Experimentally, high oxygen concentrations interfere with the formation or function (or both) of surfactant./48/ This probably occurs through the damaging effect of high

oxygen tensions on the type II alveolar epithelial cell. When high inspired oxygen concentrations are required, ventilation must be regulated to promote surfactant production rather than impede its replacement. Rapid breathing, large or small tidal volumes and edema formation all interfere with surfactant production or function. However, avoidance of extremes in lung volumes and positive end-expiratory pressure appear to generate its production./14,16,49-51/

Positive End-Expiratory Pressure

Because of the dangers of oxygen toxicity and the desire of the physician to improve arterial oxygen tensions in the critically ill patient, methods have been devised to increase oxygen tension at lower inspired oxygen concentrations. This consists of maintaining a small end-expiratory pressure with the hope of keeping "unstable" alveoli open and improving oxygen uptake. While this technique is not new it has gained resurgence largely from the efforts of Asbaugh and his associates./14/

The role of end-expiratory pressure, or continuous positive pressure breathing (CPPB), in prolonged mechanical ventilation is still debatable./14,36-38/ CPPB has been shown to decrease alveolar-arterial oxygen gradients in some disease states./14,36/ It does this by increasing functional residual capacity, shifting interstitial pulmonary water, increasing diameter of large and small airways and improving the distribution of alveolar ventilation./37,52/ In addition, there is a decrease in pulmonary blood flow and as a result the over-all ratio of ventilation to perfusion is increased. CPPB, however, is only effective when the increase in alveolar pressure is not transmitted to the intrapleural space. In diseases such as adult respiratory distress syndrome or "shock lung" it may be useful; however, in pulmonary emphysema, where elastic recoil is reduced, it could be disastrous.

Although the arterial oxygen tension may improve with CPPB, reductions in cardiac output secondary to obstruction of venous return may actually lead to a net decrease in tissue oxygenation./38/ For this reason, Kumar and associates /36/ have recommended expanding plasma volume in patients undergoing

CPPB to prevent severe reductions in cardiac output. If this is done the physician should be aware that he may be increasing pulmonary water and allowing transudation of fluid into alveolar spaces, and thereby actually reducing oxygen uptake. For all of these reasons judicious monitoring of patients on CPPB includes not only determination of A-aDO2 gradients, but cardiac output. In addition to reductions in cardiac output, CPPB is associated with an increased incidence of pneumothorax secondary to alveolar rupture./36/ This danger increases as higher end-expiratory pressures are used. However, the danger may be partially avoided by using a wide bore tube attached to the exhalation port of the respirator with the free end immersed in water to a desired depth (5-15 cm). In contrast, expiratory flow impedence valves may cause dangerously high end-expiratory pressures when the patient coughs or strains./36,53/

As more data are accumulated on positive end-expiratory pressure the physician will have a clearer idea when it is indicated. Today, however, its use should be restricted to patients with poorly compliant lungs where high inspired oxygen concentrations (above 60 percent) do not allow an adequate arterial oxygen tension (50-60 mm Hg). When it is used, cardiac output should be measured before and during CPPB and the physician should be ready to cope with the dangers of pneumothorax.

References

1. Campbell EJM: Respiratory failure. Brit Med J 1:1451, 1965
2. Bigelow DB, Petty TL, Asbaugh DG, et al: Acute respiratory failure. Med Clin N Amer 51:323, 1967
3. Williams MH: Ventilatory failure. Medicine (Baltimore) 45:317, 1966
4. Williams MH, Shim CS: Ventilatory failure. Amer J Med 48:477, 1970

5. Asmundson T, Kilburn KH: Complications of acute respiratory failure. Ann Intern Med 70:487, 1969
6. Campbell EJM: The management of acute respiratory failure in chronic bronchitis and emphysema. Amer Rev Resp Dis 96:626, 1967
7. Filley GF: Pulmonary Insufficiency and Respiratory Failure. Philadelphia: Lea and Febiger, 1967
8. Bendixen HH, Egbert LD, Hedley-Whyte, et al: Respiratory Care. St. Louis: CV Mosby Co, 1965
9. Lyons HA: Respiratory acidosis. Diagnosis and management. Med Clin N Amer 51:293, 1967
10. Sheldon GP: Pressure breathing in chronic obstructive lung disease. Medicine 42:197, 1963
11. Young JA, Crocker D: Principles and Practices of Inhalation Therapy. Chicago: Year Book Medical Publishers, Inc., 1970
12. Billingham M, Eldridge F: Use of a pressure-cycled respirator (Bird) in respiratory failure, due to severe obstructive pulmonary disease. Ann Intern Med 70:1121, 1969
13. Weiss EB, Dulfano MJ: Controlled ventilation with intermittent positive pressure breathing in the management of acute ventilatory failure associated with chronic obstructive pulmonary disease. Ann Intern Med 67:556, 1967
14. Asbaugh DG, Petty TL, Bigelow DB: Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. J Thorac Cardiovas Surg 57:31-41, 1969
15. Murray JF: Shock lung. Pres Conc Intern Med 4: 1971
16. Faridy EE, Permutt S, Riley RL: Effects of ventilation on surface forces in excised dogs' lungs. J Appl Physiol 21:1453, 1966
17. Sladen A, Lover MB, Pontoppidan H: Pulmonary complications and water retention in prolonged mechanical ventilation. New Eng J Med 279:448, 1968
18. Asmundsson T, Kilburn KH: Survival of acute respiratory failure - A study of 239 episodes. Ann Intern Med 70:471, 1969
19. Pontoppidan H, Hedley-Whyte J, Bendixen HH, et al: Ventilation and oxygen requirements during prolonged artificial ventilation in patients with respiratory failure. New Eng J Med 273:401, 1965
20. Radford EP Jr: Ventilation standards for use in artificial respiration. J Appl Physiol 7:451, 1955

21. Radford EP Jr, Ferris BJ, Kriete BC: Clinical use of a nomogram to estimate proper ventilation during artificial respiration. New Eng J Med 251:877, 1954
22. Suwa K, Bendixen HH: A nomogram for dead space requirement during prolonged artificial ventilation. Anesthesiology 29:1206, 1968
23. Lipschultz AS, Zisent I, Wasserman K: A nomogram for predicting appropriate minute ventilation in respiratory failure. Presented at UCLA interhospital research conference, Jan, 1970
24. Severinghaus JW, Bradley AF: Electrodes for blood $Pa0_2$ and $PaCO_2$ determination. J Appl Physiol 13:515, 1958
25. Robin ED: Abnormalities of acid-base regulation in chronic pulmonary disease with special reference to hypercapnia and extracellular alkalosis. New Eng J Med 268:977, 1963
26. Suskind M, Rahn H: Relationship between cardiac output, ventilation and gas transport with particular reference to anesthesia. J Appl Physiol 7:59, 1954
27. Addington WW, Kettel LJ, Cugell EW: Alkalosis due to mechanical hyperventilation in patients with chronic hypercapnia. Amer Rev Resp Dis 93:736, 1966
28. Kilburn KH: Shock seizures and coma with alkalosis during mechanical ventilation. Ann Intern Med 65:977, 1966
29. Ayres SM, Grace WJ: Inappropriate ventilation and hypoxemia as causes of cardiac arrhythmias. Amer J Med 46:495, 1969
30. Schwartz WB: Role of anions in metabolic alkalosis. New Eng J Med 279:630, 1968
31. Schwartz WB: Editorial: Evaluation of acid-base equilibrium in pulmonary insufficiency. Amer J Med 41:163, 1966
32. Eldridge F: Blood lactate and pyruvate in pulmonary insufficiency. New Eng J Med 274:878, 1966
33. Mithoefer JC, Runser RH, Karetzky MS, et al: The use of sodium bicarbonate in the treatment of acute bronchial asthma. New Eng J Med 272:1200, 1965
34. Kilburn KH: Movements of potassium during acute respiratory acidosis and recovery. J Appl Physiol 26:679, 1966
35. Bates DV, Macklem PT, Christie RV, et al: Respiratory Function in Disease. Philadelphia: WB Saunders Co, 1971 pp 50-60

36. Kumar A, Kalke KJ, Geffin B, et al: Continuous positive-pressure ventilation in acute respiratory failure. New Eng J Med 283:1430, 1970
37. Lenfant C: Revival of an old battle: Intermittent versus continuous positive-pressure breathing. Editorial. New Eng J Med 283:1463, 1970
38. Lutch J, Glazier JB, Murray JF, et al: Effects of continuous positive-pressure breathing (CPPB) on systemic oxygen transport and tissue oxygenation. Presented at the American Thoracic Society Meetings, Los Angeles, May 19, 1971
39. Kumar A: Objectives of oxygen therapy. Letter to Editor. New Eng J Med 284:917, 1971
40. Singer MM, Hamilton WK: Correspondence: Objectives of oxygen therapy. New Eng J Med 284:917, 1971
41. Singer MM, Wright MM, Stanley LK: Oxygen toxicity in man. A prospective study in patients after open heart surgery. New Eng J Med 283:1473, 1970
42. Barber RE, Lee J, Hamilton WK: Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. New Eng J Med 283:1478, 1970
43. Hyde RW, Dawson AJ: Unintentional iatrogenic oxygen pneumonitis. Response to therapy. Ann Intern Med 71:517, 1969
44. Van de Water Jr, Kagy KS, Miller IT, et al: Response of the lung to 6-12 hours of 100 percent oxygen inhalation in normal man. New Eng J Med 283:621, 1970
45. Nash GB, Blennerbassett JP, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. New Eng J Med 276:368, 1967
46. Miller WW, Waldhausen JA, Rashkind WJ: Comparison of oxygen poisoning of the lung in cyanotic and acyanotic dogs. New Eng J Med 282:943, 1970
47. Winter PM, Gupta RK, Michalski AH: Modification of hyperbaric oxygen toxicity by experimental venous admixture. J Appl Physiol 23:954, 1967
48. Morgan TE, Finley TN, Huber GJ: Alterations in pulmonary surface active lipids during exposure to increased oxygen tensions. J Clin Invest 44:1737, 1965
49. Clements JA, Fisher HK: The oxygen dilemma. Editorial. New Eng J Med 282:976, 1970
50. Hedley-Whyte J: Causes of pulmonary oxygen toxicity. Editorial. New Eng J Med 283:1518, 1970

51. Tierney PF: Pulmonary surfactant in health and disease. Dis Chest 47:247, 1965
52. Parsons EF, Travis K, Shore N, et al: Effects of positive-pressure breathing on distribution of pulmonary blood flow and ventilation. Amer Rev Resp Dis 103:356, 1971
53. Colgan FJ, Barrow RE, Fanning GL: Constant positive-pressure breathing and cardiorespiratory function. Anesthesiology.34:145, 1971

Personally I am always ready to learn, although I do not always like being taught.

—Winston Churchill

HOSPITAL-ACQUIRED GRAM-NEGATIVE PNEUMONIAS

LTC Edward E. Mays, MC, USA

Gram-negative bacilli are frequently found in oropharyngeal cultures of ill patients./1/ In a report by Meyers and workers /2/, exposure to the hospital environment resulted in an increased prevalence of positive cultures, so that by 96 hours of hospitalization, 55 percent of moribund patients and 19 percent of moderately ill patients had become colonized by gram-negative bacilli. This increased prevalence was not correlated with prior antibiotic therapy or inhalation therapy administration. Normal subjects, on the other hand, are infrequently colonized by gram-negative bacteria even in the hospital environment. In fact, even massive exposure of normal subjects to gram negative organisms does not result in oropharyngeal colonization./2/ While it is widely known that pharyngeal flora may often be recovered from the lower airways of patients with chronic bronchitis or cystic fibrosis, the lower respiratory tract is kept sterile in physiologically normal subjects by innate defenses.

The known mechanisms responsible for clearance of bacteria from the pharynges and lungs are phagocytosis by macrophages and removal by the mucociliary blanket. Clearance rates are dependent upon the result of the interaction of the extracellular substances emitted by the bacteria and the defense mechanisms of the macrophages./3/ These clearance rates vary with different bacterial species. Pulmonary clearance is presumably impaired, and allows for superinfections with gram-negative organisms, in patients with underlying dysfunction in host resistances such as occurs in malignancy, advanced age, general debility, treatment with antibiotic or cytotoxic drugs, chronic pulmonary disease, surgical instrumentation /4/, or with alcoholism, heart disease, renal disease, or diabetes mellitus./5/ Such conditions are common in hospitalized patients, and serve either to compromise physical (mucous membrane) defense barriers against infection, or to impair humoral or cellular phagocytic function./6/

Bacteria present in the oropharynx frequently enter the lungs either by aspiration during sleep /7/ or by agonal or accidental aspiration. In postmortem studies of lungs, gram-negative bacteria are the most frequent category found, in higher prevalence and concentrations when associated with bronchitis or pneumonia./8/

Thus, in hospitalized patients, the normal pharyngeal flora may evolve into a predominantly gram-negative population. If defense mechanisms are impaired, the small numbers of these bacteria normally present in the lungs may proliferate, leading to the development of nosocomial gram-negative bacillary pneumonia./8/ Alternatively, aspiration from the nasopharynx, bacteremia with seeding of the lungs from a distant focus, and blunt or penetrating chest trauma may be the more usual mechanisms for the production of these pneumonias./5/

Whatever the mechanism of onset, it seems clear from a number of reports that the major infectious disease problems in most hospitals today are those that occur in the hospital, and that gram-negative bacilli are the major bacteria involved /6, 9/, supplanting the well-known staphylococcal infections of a few years back.

Reports from several surveys indicate that nosocomial infections occur in 3.5 to 15.5 percent of hospital populations./6/ Feingold /6/ reported that hospital-acquired respiratory infections develop in approximately five percent of patients admitted to general hospitals. Gram-negative pneumonias generally account for about 60 percent of these pneumonias diagnosed /9/, while 30 percent are gram-positive, and the remainder are of unproven etiology. McNamara /10/ calculated, from data obtained at the University of Kentucky teaching hospital, that the risk of developing a nosocomial infection of any type is six percent of all hospital admissions. Of these, the respiratory tract led all other sites in frequency of infections with 39 percent. Gram-negative infections were four times as frequent as gram-positive infections. Gram-positive colonization, without apparent infection, was more frequent, however. Escherichia coli, Klebsiella and Pseudomonas each accounted for about 15 percent of nosocomial infections, and mixed gram-negative with gram-positive or other gram-negative organisms accounted for another 20 percent of these infections. On the adult

medical and surgical services, 75 percent of nosocomial infections were gram-negative, but only 45 percent were on pediatrics.

Many gram-negative genera have been reported to cause human pneumonias./5/ Recently, due to increased interest, a rash of such reports has been published. Now for the first time, the definition of some specific clinical differentiating features associated with the disease caused by specific bacteria has become clarified. Organisms of major importance which have been recently reported upon include E. coli /11/, Klebsiella-Enterobacter-Serratia /12-14/, Proteus /15/, Pseudomonas /16/, Bacteroides /17, 18/, and Hemophilus /19/. Other gram-negative organisms previously reported to have caused pneumonias include the genera Achromobactrum, Brucella, Chromobactum, Neisseria, Pasteurella, Paracolobactrum, Salmonella and Shigella./5/

Criteria for the definitive diagnosis of gram-negative pneumonias in most reports have been much the same as for gram-positive pneumonias: (1) isolation of the same bacteria from two or more consecutive sputa, (2) recovery of the same bacteria from blood and sputum simultaneously and, (3) isolation of a solitary or predominant organism from the pleural fluid. Presumptive diagnoses may be made by: (1) isolation of bacteria from the blood in a patient with pneumonia, (2) gram-stained evidence of a predominant or only organism, (3) compatible clinical presentation, or (4) improvement only after a specific antibiotic is given.

CHARACTERISTICS OF GRAM-NEGATIVE PNEUMONIAS

Certain characteristics of gram-negative pneumonias have clearly emerged, and may be used to stress the severity of such an occurrence, and to cause clinical suspicion of their presence so that appropriate therapy may rapidly be initiated. Differences which allow for suspicion of specific genera will be pointed out later in this outline. Gram-negative pneumonias tend to strike predominantly middle-aged men with serious underlying diseases. The over-all mortality rate is approximately 50 percent of those infected, ranging

from a low of 17 percent in pneumonias due to Proteus to a high of 80 percent in Pseudomonas pneumonias. Well-defined associated diseases or factors influence the etiology (Table I) as well as the mortality rates (Table II).

Diagnoses may be difficult to make due to contamination of sputum cultures by passage through the oropharynx during collection./5/ Sputum smears may be misinterpreted due to the fact that gram-negative bacilli often occur side-by-side with the much more visible gram-positive cocci./20/ It is therefore necessary to examine many microscopic fields in order to get a proper estimate of the quantity and variety of organisms. Moreover, gram-negative pneumonias often occur after aspiration and therefore initially may be considered as a purely chemical pneumonitis in the individual case. The internist is likely to see late untreated aspiration pneumonia cases with bacterial infection. Finally, gram-negative pneumonias may be merely manifestations of disseminated septicemia and hence mimic staphylococcal infections, or may occur as superinfections in the same site following successful penicillin therapy of pneumococcal pneumonia. A change in bacterial flora is a well-known consequence of antibiotic therapy. This phenomenon is likely to occur about the 7th day of treatment of a pneumococcal pneumonia, and to follow large dosage, combined antibiotic or broad spectrum antibiotic coverage. It is frequently accompanied by evidence of the new organism in high concentration and by definite deterioration of the patient. Klebsiella-Enterobacter infections frequently follow ampicillin therapy, and Pseudomonas, Klebsiella or Proteus infections follow cephalothin therapy./20/

Tillotsen and Finland /21/, in a prospective study of 149 patients with primary bacterial pneumonias, found that secondary pneumonias developed in 18, which resulted in 16 deaths. Gram-negative bacteria predominated in colonizations and superinfections. Colonizations by individual bacterial species was related to certain drug regimens, with high drug dosage levels, with the more severe primary pneumonias, with tracheostomy, or age over 60 years. Superinfection, however, occurred most frequently in patients who had primary lobar pneumonias, or who were treated with either aminoglycosides or broad spectrum antibiotics, with or without penicillin. Colonization by coagulase-positive staphylococci or by Pseudomonas was also more likely to progress to superinfections.

TABLE I

UNDERLYING DISEASES IN GRAM-NEGATIVE PNEUMONIAS

GENERA	UNDERLYING DISEASES HEART	LUNG	RENAL	DIABETES	ALCOHOLISM
Klebsiella-enterobacter	++	+	+	++	+++
E. coli	+++	++	++++	+++	++
Pseudomonas	+++	++++	+	+	+++
Proteus	+	+	–	–	++++
Bacteroides	++	+++	+	–	++
Hemophilus	+	++++	–	+	+

+ = estimated degree of relationship to specific infection

TABLE II

FACTORS INFLUENCING MORTALITY IN GRAM-NEGATIVE PNEUMONIAS OVER-ALL

FACTOR	TOTAL FATAL CASES (Percent)
Chronic lung disease	75
Heart disease	72
Diabetes Mellitus	47
Alcoholism	39
Positive blood culture	71
Age over 50 years	64
Two lobes involved	33
Three lobes involved	45

Diagnostic features of superinfections were recurrence of fever, increase in lower respiratory signs or symptoms, new x-ray infiltrate, increase in number of polymorphonuclear leukocytes in sputum, and salutary response to change in antibiotics.

SPECIFIC PNEUMONIAS

E. Coli Pneumonias

E. coli pneumonia tends to occur more predominantly in patients with renal disease or following instrumentation of the genitourinary or gastrointestinal tracts. The organism is clearly associated with acute or chronic renal, gallbladder, peritoneal, or appendiceal infections. It is suspect also in patients who have heart disease, diabetes, chronic lung disease or alcoholism. Patients tend to have tachycardia and continuous fevers, perhaps a reflection of endotoxin effects. Rales without consolidation are found in the lung bases, however, empyema is likely to develop late, about the 6th day. Bilirubin, serum glutamic oxaloacetic transaminase and urea nitrogen tend to be elevated, and the organism may be seen by Gram stain and recovered by culture from sputum, urine, blood or pleural fluid, all manifestations of bacteremia. The average white cell count (WBC) is 15,000 with a leftward shift in all cases. Large unilateral empyemas in a bronchopneumonia may mimic streptococcal pneumonia which, however, along with bacteroides develops empyema quite early in the course. Abscesses are rare, different from staphylococcal or Klebsiella pneumonias. In the report of Tillotson and Lerner /11/, one or more serious chronic diseases was present in every case of E. coli pneumonia. Lower lobe bronchopneumonia was seen on chest roentgenograms in practically all cases, suggesting diffuse aspiration as the etiological factor, however, recall that bacteremic spread of infection may present the same x-ray picture.

Pseudomonas Pneumonias

Pseudomonas pneumonias /16, 22/ are in general severe with a very high mortality rate, occurring in patients with

decreased bacterial resistance. Associated chronic disease is predominantly pulmonary, followed by cardiac with congestive failure, diabetes and to a lesser extent by other debility. Seventy-five percent of those effected have a preceding upper respiratory infection, and 70 percent have pharyngitis, otitis and tracheitis. The elevated temperature is continuous over 104 F in 50 percent of patients and 80 percent of them have a reversal of the diurnal curve (peak fever occurs between 6-10 A.M., rather than in the evening). Klebsiella-enterobacter infection is also said to reverse the curve. Patients are cyanotic at rest in 70 percent of cases, have a relative bradycardia, and have a copious productive cough with yellow or green sputum. The WBC is initially normal in 70 percent of cases and later rises to an average peak of 19-20 thousand cu mm. Persistent azotemia and abnormal liver function tests are usually seen. Sputum smears reveal the gram-negative bacilli, which are also recoverable from the throat, pleural fluid, blood and urina. Chest x-ray films reveal often bilateral diffuse bronchopneumonia, with distinctive nodular infiltrates with microabscesses in the posterior aspects of lower lobes. These are not seen in other gram-negative pneumonias, but are often seen in staphylococcal pneumonias. The course is prolonged, with empyema occurring usually late, in 80 percent of cases. Death may be due to shock, myocardial infarction, congestive failure or gastrointestinal bleeding, manifestations of the intense vasculitis associated with pseudomonas exotoxins./8/ Aspiration (or the use of mechanical ventilators) is probably the pathogenesis in the vast majority of cases.

Friedlander's (Klebsiella) Pneumonias

Friedlander's (Klebsiella) pneumonias occur predominantly in alcoholics and in other debilitating diseases./13/ The patient frequently has upper respiratory tract, oropharyngeal or dental pathology, suggesting aspiration as the pathogenesis. /23/ Patients are acutely ill with high fevers and cough productive of tenacious, often brick-red sputum. Hypotensive shock may be present, a factor which increases the mortality rate from 20 to 80 percent. Physical findings reveal upper lobe consolidation, often without bronchial breath sounds, and variable evidence of loss of lung volume on the same side. The organisms are present in the sputum, however, poorly stained sputum smears may show organisms resembling Diplococcus

pneumoniae, or the infection may be mixed, causing errors in rapid diagnosis and therapy. Leucopenia may be present in about 30 percent of cases and jaundice in 20 percent. Chest x-ray films show upper lobar consolidation (or superior segment of lower lobe) usually, with sharply defined interlobar fissures which may be bulging early or retracted later in the course. Early abscess formation may suggest tuberculosis, which may be excluded by acid-fast smears and tuberculin skin testing. D. pneumoniae rarely cause early abscess formation, a differentiating point in diagnosis.

Proteus Pneumonias

In Proteus pneumonias /15/, chronic lung disease, and especially alcoholism with an enlarged liver, predominate as underlying factors. Patients frequently have pharyngitis or conjunctivitis, again suggesting aspiration as the source of organisms, and the pneumonia is relatively benign. Approximately 50 percent of subjects have delirium tremens or other manifestations of altered consciousness, and almost all patients have had a preceding respiratory infection. The sputum smear is usually positive, although gram-positive cocci frequently coexist on the smear. Patients have upper lobe and posterior segment dense pulmonary consolidations with abscesses and tracheal shifts toward the side of involvement, and may have associated metastatic abscesses to the central nervous system, heart, or other areas. The x-ray picture may mimic pneumonias caused by D. pneumoniae or Klebsiella. The duration of the illness is long, and sputum cultures may remain positive for long periods on antibiotics.

Bacteroides Pneumonias

Bacteroides pneumonias /17,18/ tend to occur in two or three distinct clinical situations: in older male patients with underlying lung or heart disease or alcoholism secondary to aspiration; in young females who have pelvic infections with secondary blood-borne metastases to lungs; and in patients with gastrointestinal conditions, especially large bowel disease, postoperatively. In the first category, most have had preceding upper respiratory infections, and present to the clinician in no acute distress; only 50 percent are febrile initially; 50 percent have nausea and vomiting. Patients

may have had cough and non-foul sputum for several weeks. Initial WBC is elevated with infrequent shift to the left, the sedimentation rate is often over 100 mm per hour and the average hemoglobin is 8.8 grams/100 cc. Sputum smears and pleural fluid reveal gram-negative bacilli and leucocytes; cultures must be anaerobic, and often grow out anaeropic streptococci. Chest x-ray shows minimal lower lobe pneumonitis, but massive empyema, that is often loculated. The other two presentations reveal evidence on chest x-ray of lower lobe bronchopneumonia (resembling small septic emboli) and small, early empyemas. Almost invariably these infections develop after surgery, trauma malignancy or other processes which cause necrosis of tissue or mucosal surface interruption in the gastrointestinal or pelvic areas. Preoperative bowel sterilization with non-absorbable antibiotics may actually allow the normally present Bacteroides species in the gut to be isolated in pure culture./18/

Hemophilus Pneumonias

Hemophilus pneumonias /19/ are relatively rare, and tend to occur in patients with underlying chronic obstructive airways disease or alcoholism. The organism is commonly isolated from the sputum of patients with COPD or even from normal subjects. Since most investigators have insisted on isolation of the organism from blood or empyema fluid as proof of etiology in pneumonias, cases of H. influenzae pneumonia with bacteremia have been excluded from the scrutiny of literature review, and the clinical picture is muddled. It appears that patients present with moderately severe general symptoms, a moderate leucocytosis, and a single-lobed pneumonia. Gram stained sputum smears may be misinterpreted by house officers, the gram-negative coccobacilli are frequently missed. Culture growth, however, may reveal large numbers of organisms.

THERAPY

The therapy of gram-negative pneumonias involves many considerations.

All too often the drugs are administered indiscriminately or injudiciously, routinely rather than rationally, invariably rather than selectively, or hastily rather than with appropriate deliberation. Conversely, in patients with potentially curable infections, failures in therapy result all too frequently from incorrect choice of drugs, delay in initiation or from inadequate duration of therapy, improper dosage or route of administration, adverse reactions, and failure to correct underlying abnormalities that predispose to or complicate infection. A major objective of antibacterial therapy is the elimination of viable pathogens from diseased tissues in the shortest possible time with a minimum of adverse effects and inconvenience to the patient./25/

Certain general principles /24/ which underlie all decisions regarding antimicrobial therapy are:

Appropriate therapy should be initiated after pinpointing the type and nature of the infection as well as possible, using standard smear and culture techniques. In acute infections, a physician must choose initial therapy guided only by a presumptive diagnosis.

As soon as the results of culture are available, the physician should "tailor" therapy, using bactericidal drugs when possible.

Logical choices of antibacterial agents before results of susceptibility tests are available are dependent on knowledge of the current local antibiotic susceptibility pattern of the suspect or proven organism.

Precise in vitro antibiotic susceptibility testing of pertinent bacterial isolates is essential.

Tables III and IV list some effective antimicrobial drugs and dosages.

TABLE III

EFFECTIVE ANTIBIOTICS IN SPECIFIC GRAM-NEGATIVE PNEUMONIAS /24-27/

	ANTIBIOTICS							
GENERA	KAN	POLY	AMP	KEF	CENTA	CARBENA	CHL	TCN
E. coli	±	+	±	++	+	+	...	...
Enterobacter	++	±	R	R	++	++	...	...
Klebsiella	++	±	R	++	++	R	...	...
Pseudomonas	R	++	R	R	++	±	...	...
Proteus (indole+)	±	R	R	R	++	++	...	...
Proteus mirabilis	±	R	+	±	+	++	...	...
Serratia	±	R	...	...	+	R	...	...
Paracolon	±	±	±	±	...	...	...	...
H. influenzae	...	...	+	...	...	...	+	±
Bacteroides	...	...	...	...	...	...	+	±

++ = drugs of choice, i.e. over 90% strains sensitive.
+ = most (approx 80% or more) strains sensitive; may be drug of choice.
± = intermediate; significant number (over 20%) strains resistant.
R = most all strains resistant, i.e. not inhibited by attainable serum levels of specific antibiotic.
No indicator = data incomplete or the specific antibiotic not frequently indicated.

TABLE IV

SUGGESTED DRUG DOSAGE REGIMENS /23, 24, 26, 27/

		Mild, Moderate*		Severe*	
DRUG	UNIT	INITIAL DOSE+	MAINTENANCE/ DAY‡	INITIAL DOSE	MAINTENANCE/ DAY
Cephaloridine	g	1	2	2	4
Kanamycin	g	0.5	1.5	1	2
Gentamicin	mg/kg	0.4	1.2	0.8-1.2	2.4-4
Polymyxin B	mg/kg	0.375	1.5	0.625	2.5
Ampicillin	g	0.5	2	1-2	4.8
Carbenicillin	g	1	4	6	24-30

* = degree of infection.
+ = intravenously, except in non-hypotensive gentamicin patients.
‡ = Cephaloridine b.i.d. doses; all others q/6h doses.

A number of other drugs as indicated and several surgical procedures may be necessary in the treatment of these seriously ill patients, as the prognosis is directly related to the severity of underlying or associated illness. Table II. Digitalis, insulin, vasopressors, blood transfusions or hydrocortisone may be prescribed as indicated. Tracheotomy, pericardiocentesis, lumbar puncture, bronchoscopy, thoracentesis, tube or open thoracotomy, liver biopsy, or even exploratory laparotomy are examples of procedures which may prove necessary for good reasons./5/

Despite appropriate antibiotic therapy and other supportive measures, these pneumonias due to gram-negative bacilli may cause long serious illness with prolonged courses, residual pulmonary damage, and high fatality rates.

References

1. Johanson WG, Pierce AK, Sanford JP: Changing pharyngeal bacterial flora of hospitalized patients. New Eng J Med 281:1137, 1969
2. Meyers CE, James HA, Zippin C: The recovery of aerosolized bacteria from humans. I. Effects of varying exposure, sampling times, and subject variability. Arch Environ Health 2:384, 1961
3. Jackson AE, Southern PM, Pierce AK, et al: Pulmonary clearance of gram-negative bacilli. J Lab Clin Med 69:833, 1967
4. Lepper MH: Opportunistic gram-negative rod pulmonary infections. Dis Chest 44:18, 1963

5. Tillotson JR, Lerner MA: Pneumonias caused by gram-negative bacilli. Medicine 45:65, 1966
6. Feingold DS: Hospital-acquired infections. New Eng J Med 283:1384, 1970
7. Amberson JB: Aspiration bronchopneumonia. Int Clin 3:126, 1937
8. Mays BB, Thomas GD, Leonard JS Jr, et al: Gram-negative bacillary necrotizing pneumonia: A bacteriologic and histopathologic correlation. J Infect Dis 120:687, 1969
9. Thoburn R, Fekety FR, Cluff LE, et al: Infections acquired by hospitalized patients. Arch Intern Med 121:1, 1968
10. McNamara MJ, Hill MC, Balows A, et al: A study of the bacteriologic patterns of hospital infections. Ann Intern Med 66:480, 1967
11. Tillotson JR, Lerner M: Characteristics of pneumonias caused by E. coli. New Eng J Med 277:115, 1967
12. Eickhoff TC, Steinhauer BB, Finland M: The Klebsiella-Enterobacter-Serratia Division: Clinical and epidemiological characteristics. Ann Intern Med 65:1180, 1966
13. Hoffman NR, Preston FS Jr: Friedlander's pneumonia. A report of 11 cases and appraisal of antibiotic therapy. Dis Chest 3:481, 1968
14. Ringrose RE, McKown B, Felton FG, et al: A hospital outbreak of Serratia Marcescens associated with ultrasonic nebulizers. Ann Intern Med 69:719, 1968
15. Tillotson JR, Lerner AM: Characteristics of pneumonias caused by Bacillus proteus. Ann Intern Med 68:287, 1968
16. Tillotson JR, Lerner AM: Characteristics of nonbacteremia pseudomonas pneumonia. Ann Intern Med 68:295, 1968
17. Tillotson JR, Lerner AM: Characteristics of cases with empyema. Ann Intern Med 68:308, 1968
18. Bodner SJ, Koenig MG, Goodman JS: Bacteremic bacteroides infections. Ann Intern Med 73:537, 1970
19. Johnson WD, Kaye D, Hook EW: Hemophilus influenzae pneumonia in adults. Am Rev Resp Dis 97:1112, 1968
20. Shulman JA, Phillips LA, Petersdorf RG: Errors and hazards in the diagnosis and treatment of bacterial pneumonias. Ann Intern Med 62:41, 1965
21. Tillotson JR, Finland M: Secondary pulmonary infections following antibiotic therapy for primary bacterial pneumonia. Antimicrobial agents and chemotherapy. 1968 Amer Soc Microbiol, 1969, p 326

22. Lieberson AD, Winter LW, Behnke RH, et al: Extensive pseudomonal pneumonia ultimately responding to polymyxin therapy. Amer Rev Resp Dis 100:558, 1969
23. Manfredi F, Daly WJ, Behnke RH: Clinical observation of acute Friedlander's pneumonia. Ann Intern Med 58:642, 1963
24. Parker RH, Paterson PY: Antimicrobial agents. Selection and use. J Chron Dis 21:719, 1969
25. McHenry MC: Antibacterial therapy. I. Some general considerations in regard to therapy. Cleveland Clin Quart 37:43, 1970
26. Jackson GG, Finland M (eds): International symposium in gentamicin. A new aminoglycoside antibiotic. J Infect Dis 119:(Apr-May), 1969. Complete issue.
27. Symposium on Carbenicillin: A clinical profile. Rockefeller Univ, NY, NY, Jan 24, 1970. J Infect Dis 122:(Sep), 1970. Complete issue.

SARCOIDOSIS

Etiology and Treatment

MAJ Allen S. Lipschultz, MC

Sarcoidosis is not an uncommon disorder /1,2/, however, despite its relative frequency no clear etiology has emerged. This is in part related to the confusion of other disease states with sarcoidosis, including tuberculosis, fungal diseases, leprosy, berylliosis and occasionally lymphoma and metastatic carcinoma./3,4/ Only when other known diseases have been excluded can the physician then place the label "sarcoidosis" on the patient. The process of exclusion includes complete skin testing, culturing and staining of secretions and biopsied tissues, and demonstration of non-caseating granulomata in these biopsied specimens. When possible, biopsied tissue should include the area of clinical involvement rather than more peripheral sites since these areas may yield a falsely positive diagnosis. This is particularly evident in lymph nodes draining sites of chronic infection or malignant change./3/ The specificity of the Kveim-antigen skin test which has been felt to be diagnostic for sarcoidosis now appears to be open to question./5/ Until laboratory or pathological evaluation allows a definitive diagnosis, a multiplicity of tests will still be required.

It is with these general thoughts in mind that two exciting and controversial areas of sarcoidosis are reviewed - the etiology and treatment of the disorder.

ETIOLOGY

In the 1930s and during World War II it was popularly felt that sarcoidosis was a "special phase of tuberculosis." /6,7/ However, opinion began to change when it became apparent after isoniazid was introduced in the early 1950s that antituberculotic chemotherapy was ineffective against sarcoidosis. In addition, the rapid fall in the prevalence rates for tuberculosis was not accompanied by a corresponding fall in the rates for sarcoid./8/

Subsequently investigators became interested in the concept of delayed hypersensitivity and the sarcoid reaction, and speculated as to whether or not sarcoid could be the reaction of an immunologically deficient host to injury. More recent evidence presented by Sutherland, et al /9/, strongly suggests that this reaction is acquired after the development of sarcoidosis. They /9/ studied the results of a mass bacille Calmette Guerin (BCG) vaccination trial over a 10-year span in British school children. Fifty-two of the patients followed subsequently developed sarcoidosis. There appeared to be no relationship between their pre-existing tuberculin status or prior BCG vaccination when compared to the large group who did not develop sarcoidosis. In other words, among the fifty-two patients who developed sarcoid there was a comparable distribution of BCG vaccinated, un-vaccinated and prior tuberculin reactivity when compared with the larger group without sarcoid. However, once the patients did develop sarcoid the loss of tuberculin reactivity was frequently seen. They concluded that the failure to develop hypersensitivity to tuberculin skin test antigen was therefore acquired. The group that developed sarcoidosis was not challenged with other antigenic stimuli initially, and so conclusive evidence of a normal immunologic status before the development of the disease is lacking. Israel and Sones /10/ found further support for this conclusion when 13 of 360 patients with sarcoid later developed tuberculosis. All developed positive skin tests, but then 30 percent of this group subsequently lost the ability to react to tuberculin. They concluded that sarcoidosis results in an inability to maintain tuberculin reactivity. This "acquired" defect can be demonstrated in vitro with cultured lymphocytes. When these cells are taken from patients with sarcoid during the acute phase of their illness they are unable to respond to phyto-hemagglutination-M-stimulation with blast transformation./11/

More recently research into the etiology of sarcoid has shifted back to mycobacteria, particularly the "atypical organisms". This resurgence has largely gained impetus through the exciting work of Mankiewiez and her co-workers. These reports note that most patients with sarcoid bear lysogenic mycobacteria and mycobacteriophage. These lysogenic phage-infected mycobacteria lose their acid-fast staining capacity and only after repeated passage through selected media can they be demonstrated in sarcoid granulomas. They have isolated mycobacteriophage strains from stool, serum and

biopsied material in a significant number of cases. Patients with tuberculosis will also have mycobacteriophage in these specimens. However, unlike the patients with tuberculosis, those with sarcoid lack a phage-neutralizing antibody. In the absence of antibody, phage-infected mycobacteria multiply. This group led by Mankiewiez postulates that persistence of mycobacteriophage or carrying of unrelated viruses by mycobacteria leads to depression of tuberculin reactivity similar to the depression seen in the viremia of measles.

Hirshault and co-workers /17/ recently found antibody to a herpes-like virus (HLV) in high titers in all patients with sarcoid, compared to low titers in 76 percent of controls. Persistence of virus, then, could conceivably fit with Mankiewiez's theory. Chapman and his group /18,19/ have found antibodies to atypical mycobacteria in significant titers in 80 percent of patients with sarcoid and in only three percent of controls. It is these patients with antibody to atypical mycobacteria, but lack of antibody to phage, that have sarcoidosis. Recently two other reports have given further impetus to the atypical mycobacteria as an etiologic agent. Vanke and Schwartz /20/ retrospectively evaluated patients with biopsy proven sarcoid. All were tuberculin negative. They were able to demonstrate acid-fast bacilli microscopically in 30 consecutive cases after an extremely diligent search for these organisms. In a large series of patients, Addrizzo and co-workers /21/, using a triple biopsy technique to make the diagnosis of sarcoid (scalene and mediastinal lymph nodes and lung tissue), found a 15 percent incidence of acid-fast bacilli not culturable as mycobacterium tuberculosis. Zaki, et al /22/, attempted to test the hypothesis that patients with sarcoid harbor mycobacteria and that a higher incidence of tuberculosis would therefore be seen in their intimate contacts. Using matched controls they found no difference in the incidence of tuberculosis in the relatives of sarcoid patients when compared to the control group (asthmatics)./22/ Unfortunately, their sample was small but possibly as the study continues a significant difference will appear.

Although the atypical mycobacteria are becoming increasingly more popular as the etiologic agent in sarcoidosis, questions still remain unanswered. What is the incidence of atypical mycobacteria in other nontuberculous granulomatous diseases and in diseases which can cause granulomatous reaction,

specifically lymphomas and metastatic carcinoma? When are the lysogenic phage-infected mycobacteria acquired by the host? Are they the inciting agent in sarcoid or simply a secondary invader in a susceptible host? Does the patient with tuberculosis, who later acquires sarcoid, have a significant titer of phage-neutralizing antibody which is subsequently lost before the actual development of sarcoid? Does the patient with sarcoid, who later develops tuberculosis, acquire the phage-neutralizing antibody? With the increasing number of prospective studies of patients who develop sarcoidosis, perhaps some of these questions will ne answered. However, until the disease can be reproduced with a known agent sarcoidosis will continue to be an enigma.

TREATMENT

Pulmonary Sarcoidosis

Since the etiology of sarcoidosis remains unknown, treatment of the disease is nonspecific. Sarcoidosis is clearly a disease with systemic manifestations, however, pulmonary complications are seen with the greatest frequency./1/ Nevertheless, it is the treatment of pulmonary sarcoidosis which has been subjected to the most controversy. This has occurred because (1) sarcoidosis commonly goes into spontaneous remission, and there the therapeutic results appear confusing; (2) adequately controlled therapeutic trials are lacking; (3) parameters used to judge improvement in the disease vary from one investigator to another; and (4) initial diagnostic accuracy in sarcoidosis has not been uniform from study to study.

Most studies have been retrospective /23,27/ and only a small group of patients with marked abnormalities of pulmonary function have been evaluated. In general, these studies point to improvement in pulmonary function only when the initial abnormality was moderately severe, or severe. Sharma, et al /25/, were able to demonstrate significant improvement with corticosteroids in five of thirteen patients whose initial diffusing capacity (single-breath technique) was less than 65 percent of the predicted capacity. In a similar group of eight untreated patients there was no improvement in

the diffusing capacity. Whether the diffusing capacity is a reliable parameter to follow is certainly debatable. Young and co-workers /28/ evaluated 25 patients with sarcoidosis prospectively for one to two years. Patients were alternatively placed on prednisone, 60 mg per day for one month, and 20 mg per day for another five months, or received no treatment. When they compared the two groups looking for improvement in arterial blood oxygen tension, diffusing capacity or vital capacity, they found no significant difference between these groups. However, their study was small and only a few patients with moderately severe to severe diseases were followed. Their conclusion, however, was that steroids did not seem to alter the early course of pulmonary sarcoidosis.

Other studies /29,30/ cite the clinical, or radiological improvement following steroids, despite the failure of pulmonary function tests to show comparable improvement. Since steroids probably reduce inflammation in the sarcoid granuloma and enhance the fibrotic phase /25,26/ it is logical to suppose that radiologic improvement may occur since "healed" granulomas with scattered areas of fibrosis may be difficult to detect on chest roentgenograms.

From a review of these studies it would seem logical to treat patients with pulmonary sarcoidosis if there is significant hypoxemia at rest, unexplained by other causes such as underlying chronic obstructive lung disease. The level of arterial oxygen tension to become concerned about is arbitrary. However, below 80 mm. Hg at rest at sea level is clearly abnormal /31/; if the oxygen tension decreases with exercise this is further support for treatment. While the diffusing capacity may be a useful parameter in some hands /25/, it can be normal when other tests of pulmonary function are abnormal. In addition, the method of performing the diffusing capacity is subject to variations from laboratory-to-laboratory. In our hands the diffusing capacity, using single-breath technique, and related to the alveolar volume, is frequently normal in sarcoidosis while the vital capacity and arterial oxygen tension are quite abnormal.* Rather than using one parameter it would be more useful to evaluate several variables. Young, et al /28/, followed vital capacity, diffusing capacity and arterial oxygen tension and based therapeutic decisions on abnormalities of these

*Wasserman, K. Unpublished observations. Doctor Wasserman is Chairman, Division of Respiratory Diseases, Harbor General Hospital, and Associate Professor of Medicine, University of California, School of Medicine, Los Angeles.

tests. Basing an initial therapeutic decision on abnormalities in any one of these tests and following all three would be one logical approach.

Simply finding an abnormality of pulmonary function is probably not satisfactory. Evidence of progressive deterioration of these values is also felt to be necessary before treatment can be started.+ The patient with asymptomatic hilar or paratracheal adenopathy and normal pulmonary function tests at rest is clearly not a candidate for treatment. In addition, patients with chronic fibrotic pulmonary parenchymal lesions and stable pulmonary function tests, including arterial oxygen tension of more than one year, probably should not be treated.+ Patients with pulmonary parenchymal lesions, minimal symptoms and mild hypoxemia at rest are a controversial group. If their disease does not show progressive deterioration the American Thoracic Society has recommended not treating these people. The only group benefitting from therapy that has emerged from the numerous studies are patients with progressive pulmonary parenchymal involvement manifested by increasing symptoms or roentgenological changes and deterioration in pulmonary function tests, particularly arterial oxygen tension, vital capacity or diffusing capacity./22-25,28,29/

Extrapulmonary Sarcoidosis

Although controversy continues to exist in the treatment of pulmonary sarcoidosis, indications for the treatment of extrapulmonary disease are reasonably clear. Recently the American Thoracic Society has defined the group that should be treated. This group included: those with progressive impairment of visual acuity, myocardial sarcoidosis with electrocardiographic evidence of conduction defects, central nervous system sarcoidosis, persistent hypercalcemia or hypercalciuria with renal insufficiency and cutaneous sarcoidosis.+ In addition, patients with progressive renal insufficiency should be treated./32/

---

*Lipschultz: Records of pulmonary function tests in patients with sarcoidosis at LGH, 1969-1971

For most of the manifestations of sarcoidosis glucocorticoid therapy should be used. The dose of steroid is variable, but most authors have had success with 40 to 60 mg of prednisone per day for several months, and then tapering of the dose until a level is reached compatible with symptomatology and pulmonary function. Topical steroids for ocular and cutaneous sarcoidosis may also be used effectively. Immunosuppressive agents or chloroquine have been used by some if steroids have not controlled the disease, or if steroids cannot be used./33-36/ Chloroquine is particularly useful in patients who cannot be given steroids. It can also be used as an adjunct to reduce the daily steroid dose. When this is done, careful and repeated ophthalmological examination is necessary to prevent irreversible retinal changes./35/

Lastly, with the resurgence of the mycobacteria as the etiologic agent in sarcoid, prolonged treatment with anti-mycobacterial agents may again be considered in the tuberculin negative histologically proven sarcoid patient and not simply be used prophylactically in the steroid treated patient with a positive tuberculin skin test.

References

1. Mayock RL, Bertrand P, Morrison CB, et al: Manifestations of sarcoidosis. Amer J Med 35:67, 1963
2. Sitzbach LE: Current thoughts on the epidemiology and etiology of sarcoidosis. Amer J Med 39:361, 1966
3. Kent DC, Houk VN, Elliot JW, et al: The definitive evaluation of sarcoidosis. Amer Rev Resp Dis 101:721, 1970
4. Sitzbach LE: Sarcoidosis: Clinical features and management. Med Clin N Amer 51:483, 1967

5. Israel HI, Goldstein RA: Relation of the Kvein-antigen reaction to lymphadenopathy. New Eng J Med 284:7, 1971
6. Pinner M: Editorial. Amer Rev Tuberculosis 37:690, 1938
7. Pinner M: Editorial. Amer Rev Tuberculosis 54:582, 1946
8. Sitzbach LE: Sarcoidosis and mycobacteria - An editorial. Amer Rev Resp Dis 97:1, 1968
9. Sutherland I, Mitchell DN, Hart PD, et al: Incidence of intrathoracic sarcoidosis among young adults participating in a trial of tuberculosis vaccines. Brit Med J 2:497, 1965
10. Israel HL, Sones M: Sarcoidosis, tuberculosis and tuberculin anergy. Amer Rev Resp Dis 94:807, 1966
11. Buckley CE, Nagaya H, Sieker HO, et al: Altered immunologic activity in sarcoidosis. Ann Intern Med 64:508, 1966
12. Mankiewicz E: Mycobacteriophages: Isolated from persons with tuberculosis and nontuberculosis conditions. Nature 191:1416, 1961
13. Mankiewicz E, Biland J: The role of mycobacteriophages and of cortisone in experimental tuberculosis and sarcoidosis. Amer Rev Resp Dis 89:737, 1964
14. Mankiewicz E, Walberk M: Mycobacteriophages. Arch Environ Health 5:122, 1962
15. Mankiewicz E: The relationship of sarcoidosis to anonymous bacteria. Acta Med Scand Suppl 452:68, 1964
16. Mankiewicz E: Proceedings Fourth International Conference on Sarcoidosis. Paris: Masson et Cie, 1967 p 487
17. Hirshault Y, Glade P, Octavid L, et al: Sarcoidosis, another disease associated with serologic evidence for herpes-like virus infection. New Eng J Med 283:502, 1970
18. Chapman JS, Speigot M: Mycobacterial antibodies in IgA, Igm, of patients with sarcoid. Amer Rev Resp Dis 95:612, 1967
19. Chapman JS, Speight M: Further studies of mycobacterial antibodies in the sera of sarcoidosis patients. Acta Med Scand 81:176, 1964
20. Vanek J, Schwartz J: Demonstration of acid-fast rods in sarcoidosis. Amer Rev Resp Dis 101:395, 1970
21. Addrizzo JR, Minkowitz S, Lyons HA: Triple biopsy in sarcoidosis. Proceedings of the Fifth International Conference on Sarcoidosis. Prague, Czechoslovakia, June, 1969

22. Zaki MH, Addrizzo JR, Patton J, et al: Further exploratory studies in sarcoidosis: An epidemiologic investigation to compare the prevalence of tuberculosis infection and/or disease among contacts of matched sarcoidosis and asthmatic patients. Amer Rev Resp Dis 103:539, 1971
23. Emirgil C, Sobol BJ, Williams MH, Jr: Long-term study of pulmonary sarcoidosis. The effect of steroid therapy as evaluated by pulmonary function tests. J Chron Dis 22:68, 1969
24. Stone PJ, Schwartz A: Long-term study of sarcoid and its manifestation by steroid therapy: Lung function and other factors in prognosis. Amer J Med 41:528, 1966
25. Sharma OP, Colp C, Williams MH, Jr: Course of pulmonary sarcoidosis with and without corticosteroid therapy as determined by pulmonary function studies. Amer J Med 41:541, 1966
26. Boushy SF, Kurtzman RS, Martin ND, et al: The course of pulmonary function in sarcoidosis. Ann Intern Med 62:939, 1965
27. Smellie H, Arthorp GH, Marshall R: The effect of corticosteroid therapy on pulmonary function in sarcoidosis. Thorax 16:82, 1961
28. Young RL, Harkleroad LE, Lorden R, et al: A prospective evaluation of glucocorticoid therapy. Ann Intern Med 73:207, 1971
29. Sitzbach LE: Effects of cortisone in sarcoidosis. Amer J Med 12:139, 1952
30. James DG, Thomas AD: The course of sarcoidosis and its manifestation by treatment. Lancet I:1057, 1959
31. Mays EE: Blood gases as pulmonary function tests. Presented at the 21st Annual Pulmonary Disease Symposium, Fitzsimons General Hospital, September 1970
32. Committee on Therapy. Treatment of sarcoidosis. Amer Rev Resp Dis 103:433, 1971
33. Ogilvie RI, Maye M, Moore S, et al: Granulomatous sarcoid disease of the kidney. Ann Intern Med 61:711, 1964
34. Lachner MJ: Spontaneous remission or response to methotrexate in sarcoidosis. Ann Intern Med 69:1247, 1968
35. Israel HL: The treatment of sarcoidosis. Postgrad Med 46:537, 1970
36. Morse SF, Cohn ZA, Hirsch J., et al: The treatment of sarcoidosis with chloroquine. Amer J Med 30:779, 1961

I feel that the greatest reward for doing is the opportunity to do more.

—James E. Salk

NEWER CHEST DIAGNOSTIC TECHNIQUES

LTC William R. Hamaker, MC*

The following discussion is a distillation of the recent literature on diagnostic techniques used in the evaluation of patients with problems related to the pulmonary system. Many of these methods and procedures are not new by any means. What is new, however, are the refinements and improvements in their application to current diagnostic problems.

The primary aim of any diagnostic procedure should be the detection of the disease process at an earlier stage than other available methods. Its use should improve the operability and resectability rates and reduce the morbidity and mortality.

This paper provides a discussion of an up-to-date cross-sectional review of currently available diagnostic techniques.

CERVICAL-MEDIASTINAL EXPLORATION

Cervical-mediastinal exploration (CME), also termed mediastinoscopy, has become a valuable part of the diagnostic armamentarium of the thoracic surgeon. It frequently provides tissue for diagnosis and helps establish operability and resectability. The procedure is not new, but is an extension of scalene fat pad biopsy introduced by Daniels in 1949./1/ Harken et al /2/ extended the procedure combining scalene node biopsy with exploration of the mediastinal lymph nodes using a laryngoscope. In 1959 Carlens /3/ reported his technique for CME through a midline suprasternal incision to dissect, visualize and obtain tissue from mediastinal, paratracheal and subcarinal lymph nodes. The results of well over 6,000 cases have now been reported./4/

* Assistant Chief, Thoracic and Cardiovascular Surgery, Letterman

Technique

The procedure is performed under light general anesthesia. Bronchoscopy is performed as the initial part of the procedure. Appropriate biopsies and washings are taken. A suprasternal incision is then made similar to that used for tracheostomy and the paratracheal plane is explored. Blunt dissection is used to palpate abnormal nodes or fixation by tumor. A mediastinoscope is then inserted for inspection of the paratracheal and parabronchial regions. Nodes may be removed by dissection or biopsy.

Aspiration of the proposed biopsy site should always be performed. The tissue is submitted for bacteriologic and microscopic examination.

Lymphatic Drainage and Laterality of Spread

There are three groups of mediastinal lymph nodes that are inaccessible to the mediastinoscopist./6/ These are the anterior mediastinal, subaortic, and posterior subcarinal groups. In a series of 144 patients of proven carcinoma of the lung reported by Goldberg et al, one of 83 right-sided tumors had contralateral spread, and seven of 61 left-sided tumors had contralateral spread. There was an equal incidence of bilateral spread. The relationship of enlarged hilar nodes on the incidence of positive CME is noteworthy. Trinkle et al /5/ reported a 75 percent incidence of diagnosis by mediastinoscopy when there was mediastinal or hilar enlargement.

Incidence of Diagnostic CME Related to Tumor Type

Certain tumors are more likely to have mediastinal nodal involvement at the time of CME. Sarin and Nohl-Oser /7/ reported 54 of 144 (37.5 percent) patients with squamous cell carcinoma had positive CME, whereas 65 of 90 (75 percent) of patients with oat cell tumors had positive CME. Trinkle et al /5/ reported the following incidence of positive nodes at CME: anaplastic carcinoma, 60 percent; adenocarcinoma,

50 percent; and well-differentiated squamous cell carcinoma, 11 percent.

The relationship of nodal involvement to cell type as well as contra and bilateral spread as reported by Goldberg et al /4/ are given in TABLE I.

TABLE I*

INCIDENCE OF MEDIASTINAL LYMPH NODE METASTASES RELATED TO CELL TYPE

TUMOR TYPE	NO. OF PATIENTS	POSITIVE NODES	LOCATION		
			IPSI-LATERAL	CONTRA LATERAL	BI-LATERAL
Squamous Cell	52	9	6	3	...
Poorly differentiated squamous cell	64	40	...	[- - - 28 - - -]	
Oat cell	16	12	...	...	8
Adenocarcinoma	12	8	...	...	3

*From Goldberg et al /4/

Morbidity and Mortality

Large series have now been reported with an exceedingly low morbidity and mortality. In the accompanying bibliography only one death was cited. This occurred from a series of 300 patients and the cause of death in the patient who died several hours postoperatively was respiratory insufficiency./5/ Complication rates of 1.6 to 6 percent /4,8/ are the usual figures.

The chief problems associated with the procedure are bleeding, pneumothorax or pneumomediastimum, recurrent laryngeal nerve injury and chylothorax.

There have been three cases of tumor implantation reported to date./6/

Results

With respect to carcinoma of the lung, there is a wide variation in the incidence of positive return using CME. The results of several series are listed below in TABLE II.

TABLE II

INCIDENCE OF POSITIVE DIAGNOSIS IN PATIENTS WITH CARCINOMA OF THE LUNG

AUTHOR	NO. OF PATIENTS	DIAGNOSTIC CME*
		(percent)
Pinkham /10/	79	80
Sarin and Nohl-Oser /7/	296	50
Pearson /6/	239	33
Bilgutay et al /9/	50	60
Trinkle et al /5/	197	32
Delarve	217	29

*CME = cervical-mediastrinal exploration

Reliability depends on the thoroughness of the operator. Bilgutay et al /9/ reported 15 patients with negative CME who were subsequently explored and found to have carcinoma. Eight had positive mediastinal nodes which could have been diagnosed at CME. Of 38 patients with negative CME reported by Shah et al /8/ only two had positive nodes at exploration, a false negative rate of five percent. In their hands, negative CME indicates a 90 percent resectability rate and a 95 percent chance of no mediastinal node involvement. Pinkham and Torgerson /10/ cite a resection rate of 90 percent when CME is negative. Since utilizing the procedure they have reduced the incidence of exploratory thoracotomy by 30-40 percent.

In a series of 147 patients with negative CME reported by Sarin and Nohl-Oser /7/, 120 underwent thoracotomy and in only seven was it impossible to resect the tumor. Similarly, Pearson /6/ operated upon 151 patients with carcinoma of the lung after negative CME and found tumor in mediastinal nodes in eleven.

From these reports we learn that the use of CME reduces the need for exploratory thoracotomy in 27.4 to 60 percent /6,9/ and improves the resectability rate to approximately 90 percent./6,8,10/

The Problem of Positive CME

Controversy exists as to what to do with the patient found to have positive nodes at CME. Sarin and Nohl-Oser /7/ and Shah et al /8/ think that results with resection in patients with positive mediastinal nodes are no better than with irradiation alone without incurring the added surgical risks. Bilgutay et al /9/ explored three patients with positive nodes and found all to be unresectable. Twenty-seven patients with positive CME followed a rapid downhill course, and this is the usual sequence of events.

Konrad and Schulte /11/ advocate that the presence of paratracheal or parabronchial nodes is not a criterion of technical or biologic inoperability. He explored 23 with positive nodes and was able to carry out resection in 13. They believe there is a potential five year cure rate of 7-17 percent in these patients.

I think the most lucid solution to this problem is proposed by Pearson /6/ who thinks that some idea of resectability can be obtained by taking into consideration such factors as (1) gross mediastinal excension and fixation, (2) oat cell carcinoma, (3) bilateral or contralateral spread, and (4) high right pretracheal nodal involvement. He reports the results with 16 patients who had ipsilateral tracheobronchial or subcarinal nodes without gross fixation. All were given irradiation, 11 were subsequently operated and resection could be accomplished in 10. Only time will tell if combined therapy under these circumstances will improve survival rates.

CME in Benign Disease

CME is an extremely valuable tool in the diagnosis of benign pulmonary disease. In Lincoln's series /12/ the diagnosis was made in 16 of 20 (80 percent) of benign cases. Sarcoid was diagnosed in 6 of 6 and tuberculosis in 9 of 11. Trinkle /5/, on the other hand, found CME to be diagnostic in only 27 of 103 (26 percent) patients with benign lesions. Again, a high incidence of positive diagnosis of sarcoid occurred, 15 of 16. Bilgutay et al /9/ obtained a diagnosis in 34 of 40 (85 percent) of benign lesions. In 18 of 18, sarcoid was diagnosed by CME. Of interest is the fact that in 10 of the 18 a previous scalene node biopsy was non-diagnostic. TABLE III lists some of the available reports on the diagnostic value of CME in sarcoid.

TABLE III*

SARCOIDOSIS: INCIDENCE OF POSITIVE CME

AUTHOR	NO. OF PATIENTS	POSITIVE FINDINGS
		(percent)
Carlens	123	96
Nielsen and Olsen	121	95
Maassen	115	100
Jepsen	43	95
Loigren and Snellman	35	91
Palua	28	96
Patiala	25	100
Tucker	50	96
TOTAL	540	96

*From Tucker and Gartner /13/

In summary, CME can be performed with very low morbidity and mortality. It reduces the incidence of unnecessary thoracotomy by 30-40 percent and, in the presence of negative nodes, suggests a resectability of 90 percent. It is valuable in the diagnosis of benign diseases, particularly sarcoid where the diagnosis can be made in excess of 90 percent of the cases.

BRONCHIAL BRUSHING

Selective bronchial catheterization and brush biopsy has proved to be a useful technique. It has particular value in lesions which are peripherally located, i.e., those not accessible to the conventional bronchoscope. The procedure is of most value under the following circumstances: (a) patients with clinically inoperable carcinomas in whom a diagnosis is necessary before instituting radiation or chemotherapy, (b) diffuse pulmonary lesions suspected of being malignant, but the usual diagnostic methods have not provided the diagnosis, and (c) patients in whom exploratory thoracotomy represents an increased risk, but in whom the risk would be acceptable in the presence of a positive diagnosis of carcinoma of the lung./14/

Technique /15/

Nasotracheal anesthesia is performed after which an arterial catheter is passed and a Seldinger wire inserted through the catheter and positioned in the segmental bronchus. A 9-F Rothene catheter is then advanced over the guide wire. Disposable brushes, either nylon or stainless steel, are then inserted through the catheter and specimens obtained. Smears are made directly from the brushes and examined in the usual manner for cytology, acid-fast bacilli (AFB) and fungi and bacteria. Often the procedure is terminated with a selective bronchogram. Post brushing sputa are always collected and are often positive when the brush specimen was negative.

Several modifications of the technique have been developed. Having had success with transcricoid bronchography, Moskowitz and Freihofer /16/ have adapted this approach to bronchial brushing in 36 patients with no significant complications. Hattori et al /17/ have developed a brush with a flexible tip. Recently Fennessy /18/ has incorporated the flexible bronchofiberscope into his technique for bronchial brushing. This combines the advantages of direct vision and fluoroscopic guidance to obtain optimal positioning below brush biopsy.

Results

The diagnostic accuracy approaches 70 percent./19/ In a series of over 300 bronchial brushings, of which 138 were for malignant disease (117 primary lung carcinomas), Fennessy and his associates /20,21/ were able to make a cytologic diagnosis in 71 percent. Metastatic carcinoma was diagnosed in 8 of 15 (53.4 percent) and lymphoma in two of six (33 percent). AFB were obtained in three of six and aspergillus in two of two. In most of his cases of malignant disease, conventional bronchoscopy and cytology had failed to provide the diagnosis.

Faber /22/ used the procedure in 96 patients, 72 of whom ultimately were proven to have bronchogenic carcinoma. A diagnosis was made in 60 percent using the brush technique. Hattori et al /17/ diagnosed 27 of 31 peripheral carcinomas using flexible brush probes. Twelve of the lesions were less than 3 cm in size.

Fennessy /18/ reported five false positives in his series, one hamartoma and four inflammatory conditions.

Complications are few, consisting of mild bloody streaking of the sputum, transient fever, and occasional pneumothorax./15,18,20/

PERCUTANEOUS LUNG BIOPSY

Percutaneous biopsy of the lung was first performed in 1883./23/ Interest in the procedure has been reawakened by advances in cytologic diagnosis and improvements in image amplification fluoroscopy, and improvement in the treatment of its complications./23,24/ Indications for percutaneous needle biopsy vary from one institution to the next, however, the technique is used principally when the patient's general health or limited pulmonary function make thoracotomy a life threatening procedure, yet tissue is desirable for planning radiation, chemotherapy or antibiotic therapy./19,25/ Aspiration of pulmonary lesions can be utilized to obtain viable tumor cells for chemosensitivity testing./23/

Gaensler /26/, however, thinks needle biopsy should be performed only for the indications outlined eighty years ago, that is, in patients with serious pneumonias when no sputum is available, usually infants, and in patients with inoperable carcinoma, in order to facilitate chemotherapy or irradiation.

The following have been given as contraindications to percutaneous needle biopsy of the lung /19,24,26/: (1) hemorrhagic diathesis, (2) severe pulmonary hypertension, (3) patients with uncontrollable cough, or who are uncooperative, (4) advanced emphysema or bullous disease, (5) vascular malformation, (6) presence of only one functional lung, (7) hydatid cysts, and (8) people who will inevitably require thoracotomy.

Technique

The procedure can be done using a Silverman needle, or one of its modifications, under multiple view fluoroscopic guidance. Fontana et al /24/ have had excellent success with a standard 18 guage thin wall arteriographic needle. After ascertaining proper position, fluoroscopically, they apply

vigorous suction and place the aspirated material on a slide for cytologic examination. In their hands the technique has been refined to the point that the diagnosis can be made in a 1.0 cm nodule.

A posterior approach is described by Siderys and Pittman /25/ in the needle biopsy of superior sulcus tumors to confirm the diagnosis prior to the institution of preoperative irradiation therapy. Using this approach they have made the diagnosis in all of the five Pancoast's tumors they have studied.

Results

Sanders et al /23/ cited their experience with 182 percutaneous biopsies performed in 164 patients. TABLE IV.

TABLE IV*

SUMMARY OF 182 PERCUTANEOUS BIOPSIES
(164 patients)

PROBLEM	NO. PATIENTS	POSITIVE
Malignant solitary pulmonary node	63	53 (84%)
Benign solitary pulmonary nodule	12	3
Multiple pulmonary nodules	15	12
Lesions of chest wall and diaphragm	20	9
Lesions of mediastinum	21	11

*From Sanders et al /23/

Fontana et al /24/ obtained cancer cells in 78 percent of 83 cases of carcinoma of the lung. Youmans et al /28/ obtained a diagnosis in 55 of 61 patients (90 percent). In a review article Janower and Land /19/ stated that a histologic and bacteriologic diagnosis can be made in 65-85 percent of the cases in which percutaneous biopsy is used.

Complications

The chief complications of the procedure are pneumothorax and hemoptysis. Incidence of these is cited from four series in TABLE V.

TABLE V

COMPLICATIONS OF PERCUTANEOUS BIOPSY

SERIES	NO. PATIENTS	PNEUMO	REQUIRE Rx	HEMOPTYSIS
		← *percent* →		
Sanders et al /23/	182	30	5	...
Fontana et al /24/	100	57	17	6
Anderson et al /30/	335	48	48	5
Youmans et al /28/	100	...	...	23

In the diagnosis of diffuse lung disease Youmans et al /28/ prefer the second intercostal space anteriorly and incorporated the routine use of a chest tube to under water seal drainage into the technique. One-third of the patients had some air leak, the longest lasting five days.

An occasional death occurs as a result of the procedure./19/

A useful application of needle biopsy has been the intracavitary instillation of medications. Castellino et al /29/ reported a case of pulmonary aspergillosis in a patient who had undergone cardiac transplantation. The diagnosis was made by needle biopsy, following which a catheter was inserted into the cavity and left in place for long-term irrigation with amphotericin-B and sodium iodide.

Anderson, with his associates /30,31/, recently reported his experience with more than 300 consecutive cases of transbronchoscopic lung biopsy in the diagnosis of diffuse pulmonary disease. A Holinger flexible biopsy forceps was inserted into the peripheral portion of the lungs, generally the basilar segments, without fluoroscopic guidance and several biopsy

specimens obtained. Tissue sufficient for diagnosis was obtained in 80 percent. More recently the incidence of insufficient tissue for diagnosis has been reduced to 12 percent. Complications occurred in 14 percent. Twenty-four required insertion of a chest tube, less than two percent had moderate bleeding and mediastinal emphysema was seen in one percent.

RADIOISOTOPES

Improvements in methodology and ever widening application of the injection or inhalation of radioactive materials has improved the diagnostic capability of the physician.

Radioactive lung scans depend upon the lodgement of radioactive particles, generally 15 to 55 μ in size within the capillary bed./37/ Macroaggregates of albumin, ^{131}Iodine-tagged, (^{131}I-MAA) have been the standard, however, considerable work is going on in the development of additional materials. Indium 113m is being evaluated for perfusion scanning. It has a 390 kev gamma emission and a physical half life of 1.7 hours. Because of its short half life and almost pure gamma emission, multimillicurie amounts may be given without undue patient radiation exposure./32/

Technetium (99m) pertechnetate (^{99m}Tc) is being used more frequently. One hundred percent of the ion is incorporated into particles varying from 10-40 μ in diameter. Ninety-six percent of the particles are initially distributed throughout the lungs. Virtually no pulmonary pathology, chemical toxicity pyrogenicity, liver disease, hypersensitivity, or altered lung physiology has been noted after injection./33/

Intravenous xenon is relativelt insoluble in blood and tends to be cleared from the pulmonary capillary blood into the alveolar gas in a single circulation through the lungs, making it a useful agent.

Inhalation scanning consists of the administration of radioaerosols under positive pressure or ultrasonic nebulizer. A useful technique is the administration of ^{99m}Tc sulphur colloid by inhalation, and ^{131}I-MAA for perfusion. The 140 kev band in the former and 364 kev for the latter permits easy separation in combined ventilation-perfusion scanning techniques./32/

Scans frequently provide more information than chest roentgenograms alone, and are particularly useful in the clinical evaluation of patients when it becomes important to explain symptoms that are out of proportion to the roentgenographic abnormalities. In patients with inoperable carcinoma reviewed by Tauxe et al /34/ the scan findings appeared to be disproportionately more severe than those seen on plain x-ray. Using ^{99m}Tc and rapid serial scan technique, Conway and Sherman /35/ were able to correlate the phase of flow with the type of lesion encountered. The first, or pulmonary arterial phase, demonstrated vascular lesions. The second phase was helpful in delineating solid lesions, and the third, or late phase, tended to outline cysts or necrotic tumors.

Combined organ scans determine the spatial relationship of lung, liver and diaphragmatic level to each other. For example, a lung scan in conjunction with a liver scan has value in diagnosing ruptured diaphragm, elevated diaphragm, or subdiaphragmatic abscess. Also, a combined lung and heart scan is helpful in diagnosing pericardial effusion and cardiac dilatation./32/

Gold(^{198}Au), which is a beta emitter with a half life of 2.69 days, outlines the normal liver tissue and detects the presence of space occupying lesions. With an approximate dose of 100 millicurie (mc) 60-94 percent is concentrated in the liver and 6-15 percent in the spleen. The technique can detect hepatic nodules as small as 2.0 cm depending on their location and the type of equipment used./36/

The single breath ^{133}Xenon test is being incorporated into pulmonary function tests since it gives important information regarding the distribution of gases, particularly when attempting to localize large bullae./37/

It must be remembered, however, that scans are adjunctive aids and therefore should be interpreted in light of all available clinical data and and the findings on chest x-ray.

FLEXIBLE BRONCHOFIBERSCOPE

Improvements in the visualization of intrabronchial lesions have occurred with the development of a flexible bronchoscope utilizing a fiberoptic system. Currently available are the Machida and Olympus flexible bronchofiberscopes. These instruments provide for bronchial brushing and biopsy under direct vision. In addition, photography and cinematography units can be adapted for permanent records and teaching purposes.

The flexible bronchofiberscope has markedly increased the visible range, especially in the upper lobes. Subsegmental bronchi up to the fourth order can be easily visualized.

In a series of 360 cases of proven bronchogenic carcinoma reported by Ikeda /38/ the lesion could be visualized in 159 (44.2 percent) using the standard bronchoscope, however, using the flexible fiberscope, it could be seen in 299 (83.1 percent).

TANTALUM BRONCHOGRAPHY

Work is being done to improve bronchography in terms of ease of performance and quality of films. Powdered tantalum instilled by insufflation has been tried with some success. The advantages of tantalum include a lack of toxicity, the fact that tantalum is 25 times more radiopaque than iodinated compounds, and that it adheres firmly to the bronchial mucosa and is not dispersed by respiratory maneuvers. It clears rapidly and has caused no deleterious effects./39,40/

Tantalum proved to be a superior tracheogenic contrast material in ten patients being evaluated for tracheal stenosis. /41/ Further clinical experience will determine whether tantalum will replace currently used iodinated compounds. It would appear that tantalum may be superior in the evaluation of lesions of the trachea and larger order bronchi.

References

1. Daniels AC: A method of biopsy useful in diagnosing anterior intrathoracic diseases. Dis Chest 16:260, 1949
2. Harken DE, Black H, Clauss R, et al: A simple cervico-mediastinal exploration for tissue diagnosis of intrathoracic disease with comments on the recognition of inoperable cancer of the lung. New Eng J Med 251:1041, 1954
3. Carlens E: Mediastinotomy: A method for inspection and tissue biopsy in the superior mediastinum. Dis Chest 36:343, 1959
4. Goldberg EM, Glicksman AS, Khan FR, et al: Mediastinoscopy for assessing mediastinal spread in the clinical staging of carcinoma of the lung. Cancer 25:347, 1970
5. Trinkle JK, Bryant LR, Hiller AJ, et al: Mediastinoscopy - experience with 300 consecutive cases. J Thorac Cardiovasc Surg 60:297, 1970
6. Pearson FG: An evaluation of mediastinoscopy in the management of presumably operable bronchial carcinoma. J Thorac Cardiovasc Surg 55:617, 1968
7. Sarin CL, Nohl-Oser HC: Mediastinoscopy; a clinical evaluation of 400 consecutive cases. Thorax 24:735, 1969
8. Shah HH, Lambert CJ, Paulson DL, et al: Cervical mediastinal lymph node exploration for diagnosis and determination of operability. Ann Thorac Surg 5:15, 1968
9. Bilgutay AM, Jensen NK, Schmidt WR, et al: Mediastinoscopy. J Thorac Cardiovasc Surg 57:841, 1969
10. Pinkham RD, Torgerson AC: Mediastinoscopy: An important adjunct in the diagnosis and treatment of intrathoracic lesions. Amer J Surg 118:562, 1969

11. Konrad RM, Schulte HD: Mediastinoscopy in assessing the operability of carcinoma of the bronchus. Germ Med Month 14:547, 1969
12. Lincoln JCR, Provan JL: Mediastinoscopy in the diagnosis of nonmalignant disease. J Thorac Cardiovasc Surg 60:144, 1970
13. Tucker JA, Gartner W: Mediastinoscopy with special reference to the diagnosis of sarcoid. Ann Otol Rhinol Laryngol 79:937, 1970
14. Fry WA, Manalo-Estrella P: The technical details of bronchial brushing. J Thorac Cardiovasc Surg 60:636, 1970
15. Fry WA, Manalo-Estrella P: Bronchial brushing. Surg Gynec Obstet 130:1, 1970
16. Moskowitz M, Freihofer A: Seldinger brush biopsy: A synthesis of techniques. Chest 57:426, 1970
17. Hattori S, Matsuda M, Sugiyama T, et al: Cytologic diagnosis of early lung cancer: An improved TV brushing method, and a review of negative results. Dis Chest 48:123, 1965
18. Fennessy JJ: Bronchial brushing. Ann Otol Rhinol Laryngol 79:924, 1970
19. Janower ML, Land RE: Lung biopsy; bronchial brushing and percutaneous puncture. Radiol Clin N Amer 9:73, 1971
20. Fennessy JJ, Fry WA, Manalo-Estrella P, et al: The bronchial brushing technique for obtaining cytologic specimens from peripheral lung lesions. Acta Cytol 14:25, 1970
21. Fennessy JJ: Bronchial brushing and transbronchial forceps biopsy of pulmonary lesions. Dis Chest 53:377, 1968
22. Faber LP: Discussion of Reference 14. J Thorac Cardiovasc Surg 55:659, 1970
23. Sanders DE, Thompson DW, Pudden BJE: Percutaneous aspiration lung biopsy. Can Med Assoc J 104:139, 1971
24. Fontana RS, Miller WE, Beabout JW, et al: Transthoracic needle aspiration of discrete pulmonary lesions. Experience in 100 cases. Med Clin N Amer 54:961, 1970
25. Siderys H, Pittman JN: Percutaneous needle biopsy of the lung in cases of superior sulcus tumor. J Thorac Cardiovasc Surg 53:716, 1967
26. Gaensler EA: Diagnostic techniques in diffuse or miliary lung disease: Experience with 381 patients. Advances Cardiopulm Dis 3:81, 1966

27. Stevens GM, Lillington GA, Weigen JF: Needle aspiration biopsy of localized pulmonary lesions. Calif Med 106:92, 1967
28. Youmans CR Jr, Middleton JW, Derrick JR, et al: The technique of percutaneous needle biopsy for diffuse lung disease. Southern Med J 61:1023, 1968
29. Castellino RA, Goldstein HM, Stinson EB, et al: Needle aspiration biopsy technique in pulmonary disease. JAMA 213:463, 1970
30. Anderson HA, Fontana RS, Sanderson DR, et al: Transbronchoscopic lung biopsy in diffuse pulmonary disease: Results in 300 cases. Med Clin N Amer 54:951, 1970
31. Anderson HA: Lung biopsy via the bronchoscope. Ann Otol Rhinol Laryngol 79:933, 1970
32. Quinn JL III: Techniques and diagnostic possibilities of lung scanning. Advances Cardiopul Dis 4:161-174, 1969
33. Ficken V, Halpern S, Smith C Jr, et al: ^{99m}Tc sulfur colloid macroaggregates. Radiology 97:289, 1970
34. Tauxe WN, Carr DT, Thorsen HC: Perfusion lung scans in patients with inoperable primary lung cancer. Mayo Clin Proc 45:337, 1970
35. Conway JJ, Sherman JO: Evaluation of chest masses in children with early and delayed radionuclide angiography. Amer J Roentgenol Radium Ther Nucl Med 108:575, 1970
36. Mason GR, Fish V, Jamplis R: The use of radioactive gold (^{198}Au) liver scan in the diagnosis of basilar thoracic lesions. Ann Thorac Surg 9:189, 1970
37. Comroe JH Jr, Nadel JA: Screening tests of pulmonary function. New Eng J Med 282:1249, 1970
38. Ikeda S: Flexible bronchofiberscope. Ann Otol Rhinol Laryngol 79:916, 1970
39. Dilley RB, Nadel JA: Powdered tantalum: Its use as a roentgenographic contrast material. Ann Otol Rhinol Laryngol 79:944, 1970
40. Comroe JH Jr, Nadel JA: Screening tests of pulmonary function. New Eng J Med 282:1249, 1970
41. Hinchcliffe WA, Zamel N, Fishman NH, et al: Roentgenographic study of the human trachea with powdered tantalum. Radiology 97:327, 1970

Where there is an unknowable there is a promise.

—Thornton Wilder

PULMONARY DEFENSES AGAINST INFECTION

MAJ Philip Ziporin, MC

The lung is unique among the internal organs of the body because of its continuous and involuntary exposure to the ambient environment. As the vital organ of respiration it must come into intimate contact with the gases of the atmosphere and, along with them, any contaminating vapors and particles which elude the protective action of the upper respiratory passages. In the case of infectious agents, unlike nonliving materials, we find the unique capacity to replicate in kind and number so that, in the absence of defense mechanisms, a single organism could potentially fill or consume the lung. Yet, despite this continual inoculation, the parenchyma of normal lungs has been shown to maintain sterility /1/, with infections largely occurring during times of enhanced susceptibility.

In order to understand the concept of increased susceptibility to pulmonary infections one must first appreciate those features and mechanisms pertinent to defense of the lung, as has been outlined in two excellent review articles by Green./23/

Mechanisms of pulmonary clearance of infectious agents may be divided into (a) those that act by transport of the infectious particle out of the lung such as cough and expectoration, the mucociliary apparatus and lymphohematogenous drainage, and (b) those that act by killing, inactivating, or limiting the replication of the infectious agent. These in situ deterrents are broadly categorized as cellular and humoral factors. Cellular mechanisms include the several types of inflammatory cells, alveolar macrophages, neutrophils, monocytes, lymphocytes, plasma cells, eosinophils and the epithelioid cells of granulomatous reactions. Humoral mechanisms include circulating immune globulins of the IgG and IgM classes, secretory IgA and possibly IgE /4/, complement /5/, lytic enzymes such as lysozyme /6/, and granulocytic

enzymes, surface active agents such as lipid surfactants /7/, and interferon /8/. These defense mechanisms do not work in isolation or as separate entities but are closely interrelated and integrated in their defensive function at or near the surface of the respiratory membrane. Thus, the bronchial epithelial structures work in concert with the secreted mucous fluid layer to transport particles out of the tracheobronchial tree, and the immunoglobulins facilitate function of cells such as blood leukocytes and alveolar macrophages.

Within this schema certain elements appear dominant. Certainly an effective cough mechanism, one of the two modes of transport, is critical as is the other mode — an intact, functioning mucociliary system. On the local level, the combined activities of phagocytes and immune resources predominate. The latter two appear to be most significant.

The Particulate Nature of Infectious Agents

The common denominator of disease induction in the lung is the inhaled particle, since most pulmonary infections are established via the airborne route by small solid or liquid particles which settle out from suspension in the airstream within the lung. Since the airstream follows the branching alveolar pathway, particles are not handled uniformly but are governed by the physical laws of inertia, sedimentation, and Brownian motion according to their particular size./9/ Figure 1.

Inhaled particles must first survive or penetrate the aerodynamic filtration mechanism of the upper respiratory tract and tracheobronchial tree. Incoming air is subjected to considerable turbulence in the nasal passages and then to a sharp change in the direction of flow as the airstream recurves through the pharynx and is repetitively bifurcated along the tracheobronchial tree. The resulting turbulence leads to impaction of large particles on the surface lining by inertial forces. As the airstream reaches the periphery of the bronchial tree, its velocity drops rapidly, inertial forces subside and gravitational forces begin to exert a

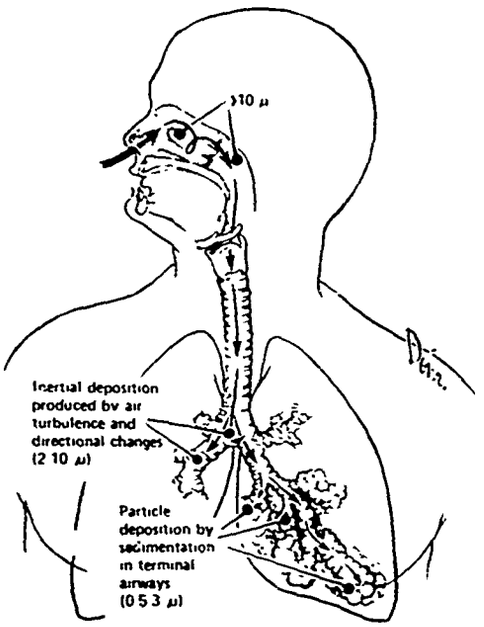

Fig. 1. Illustration of pulmonary defense mechanisms: aerodynamic filtration of particles. This concept was diagrammed in the article by Green. /3/

prominent effect./3/ As an approximation, particles of 0.5 to 2.0 u settle out at the bronchiolar to alveolar levels largely as a result of Brownian action; particles from about 2.0 to 10.0 u sediment on the tracheobronchial tree, and particles above this size impinge on the pharynx or nasal cavity. Particles much smaller than 0.2 to 0.3 u show no appreciable deposition and are subsequently exhaled./9/ Since the usual infectious aerosol is heterogenous in terms of particle size infectious agents frequently bypass transport mechanisms and, therefore, the maintenance of a disease-free parenchyma ultimately rests on in situ control measures (as previously mentioned, phagocytes are aided by a functioning immune system).

The remainder of this paper will describe this functioning immune system, first considering the primary

alveolar phagocyte — the alveolar macrophage; secondly, the humoral and cellular immune mechanisms; and lastly, a brief discussion of those factors known to limit their function (altered defense mechanisms).

ALVEOLAR MARCOPHAGES

The principal response to deposition of inhaled particles in pulmonary alveoli is made by the alveolar macrophages — large mononuclear ameboid phagocytes distinct from the cells forming the continuous alveolar epithelial layer which consists of pulmonary surface epithelial cells (Type I pneumonocytes), and great alveolar cells (Type II pneumonocytes)./10/ These cells have the unique ability to migrate over the alveolar epithelium in the absence of significant inflammation./11/ The origin of these phagocytes is still in question with suggestions including hematopoietic derivations /12/, evolution from the great alveolar cell /13/, or from mesenchymal histiocytes /14/. Sorokin /11/ recently described a series of histochemical studies comparing the latter two cell types and concluded that a greater metabolic similarity exists between the alveolar macrophages and great alveolar cells than between any other component of the alveolar wall. Pinkett et al /15/ used an ingenious approach to evaluate the question of hematopoietic contribution. They employed mouse chimeras to identify the origin of dividing macrophages in the lung alveoli. Bone marrow from histocompatible strains carrying two chromosomal markers was injected into animals whose bone marrow had been destroyed by irradiation. Four months later alveolar macrophages were harvested six hours following an injection of colchicine. By chromosomal analysis they determined that two-thirds of the dividing cells washed from the lung contained the chromosomal markers of the donor bone marrow, and the other third appeared to be of primary origin. Little can be derived from the absolute proportions since they are certainly affected by differing individual rates of mitosis, and yet of significance is the demonstration that at least a portion of the alveolar macrophages are of hematogenous origin.

Although the alveolar macrophage differs from other phagocytic cells, such as polymorphonuclear leukocytes,

monocytes and peritoneal macrophages, in many respects including intermediary metabolism and enzyme activity /16/, the mechanism of its microbicidal activity appears to be largely similar. The initial event, chemotaxis, is inaugurated either by complement or certain bacterial factors./17/ Following chemotaxis and preceding the engulfment of bacteria, the phenomenon of opsonization occurs. As discussed by Douglas /18/ opsonins generally operate through their interactions with the particle, not the phagocyte, and include IgG and IgM antibodies, complement components, noncomplement thermolabile factors and possibly basic polypeptides including lysozyme and basic polyamino acids. Subsequently phagocytosis occurs and, like other phagocytes, alveolar macrophages are rich in lysosomes. The lysosomes attach themselves to the phagosomal membrane surrounding the ingested organism and the lysosomal membranes become continuous with the phagosomal membrane followed by release of its contents. These include a wide variety of acid hydrolases, DNAase, RNAase, beta-glucuronidase, myeloperoxidase and lysozyme /18/ as well as several partially characterized substances, not necessarily enzymatic in nature such as a cationic protein that induces inflammation; the antibacterial agent, phagocyin; tissue plasminogen activator; hemolysin (or hemolysins); a mucopolysaccharide or glycoprotein "matrix"; and a protease-like permeability factor /6/. The subsequent events leading to the destruction of the organism are at present less well-defined, but include the above mentioned lytic enzymes and other bactericidal substances and the activity of the myeloperoxidase-halide-hydrogen peroxide system./19/

IMMUNE MECHANISMS

Next in line of importance, following the primary transport mechanisms and the function of alveolar macrophages, is the critical supportive role of the immune systems, both humoral and cellular. The effective humoral system consists of globulin proteins including IgA and probably IgE in the resting lung, and IgG and IgM in the inflamed lung. It is likely that in terms of defense against pulmonary infection its contribution is realized both by opsonic activity, thus enhancing phagocytes, and by direct immune injury resulting from the fixation of complement. Delayed or cellular immunity, mediated by the small lymphocyte,

has been shown by Simpson et al /20/ to be involved in recovery from infections caused by facultative intracellular parasites such as fungi, cytomegalovirus, tubercle bacilli and Listeria, organisms which survive intracellular microbicidal mechanisms. This influence is exerted by lymphocytic production of a family of effector molecules consisting of (a) migration inhibitory factor (MIF) which causes normal macrophages to agglutinate; (b) lymphocyte transforming factor (LTF) which causes normal lymphocytes to become antigen-responsive and undergo blast transformation, repeated cell division, and clonal proliferation; (c) lymphotoxin (LT), which kills target cells in culture; and (d) chemotactic factor which attracts leukocytes./21/

ALTERED DEFENSE MECHANISMS

Dysfunction of these defense mechanisms can render the lung more susceptible to infection by disturbing the equilibrium based on characteristics of the host and pathogen. Decreased phagocytic efficiency occurs in a number of conditions and disease states. A discussion of this phenomenon must include both intrinsic and extrinsic (acquired) defects. Intrinsic dysfunction relates to a group of conditions in which a defect in intraphagocytic microbicidal activity results in the prolonged intracellular survival of ingested organisms. These include chronic granulomatous disease of childhood /22/, a familial disease characterized by eczema, lymphadenopathy, hepatosplenomegaly, recurrent severe bacterial infections usually with Staphylococcus aureus, Escherichia coli, Klebsiella-Enterobacter, Salmonella and Serratia marcescens and multiple pulmonary and reticuloendothelial granulomas. In vitro studies of the neutrophils of such children have demonstrated a normal capacity to ingest bacteria, but a marked impairment of bactericidal function. /23/ The mechanism responsible for the defect is as yet unknown yet several distinct metabolic abnormalities are present including impaired oxygen utilization during phagocytosis, reduced activation of the hexose-monophosphate shunt, both resulting in decreased production of hydrogen peroxide and diminished lipid peroxidation./24/ Also, there have been reported a few cases of neutrophil myeloperoxidase

deficiency /25/ resulting in an inability to kill Candida albicans and a subnormal ability to kill Staphylococcus aureus and Serratia marcescens; and a case described by Davis et al /26/ of a demonstrated defect selective for the staphylococcus.

Acquired defects have been best studied with the use of an in vivo animal system devised by Green and Goldstein /27/ which separates the contributions of phagocytic versus transport events in the defensive response of the lung to inhaled particulate material. This is accomplished through the use of an aerosol containing radiotracer-labeled nonvirulent bacteria. Transport rates are determined by following the decline of the radiotracer tag in the lung. The bactericidal activity of the lung, a property largely due to the phagocytic activity of alveolar macrophages /28/, is determined by quantitating the change that occurs in the ratio of viable bacterial count to radiotracer count in the lung /29/. Reductions in bacterial clearance associated with ethanol ingestion, cigarette smoke, cortisone, acute hypoxia and administration of barbituates /30/, nitrogen dioxide, ozone, oxygen, immunosuppressive agents, generalized stresses (such as starvation, cold stress, and changes in barometric pressure /3/ as well as renal failure and respiratory failure when the blood pH fell below 7.2 /2/ have been described when Green and Goldstein's system /27/ was used.

It is well-recognized that immune deficiency is accompanied by a high frequency of pulmonary infection./31/ There are, as already mentioned, the two fundamental syndromes — humoral deficiency and cell-mediated deficiency. Humoral deficiency is characterized by low or absent serum immunoglobulins, poor or absent antibody response to a variety of antigens, and recurrent severe bacterial infections with high-grade encapsulated pathogens such as Pneumococci, Staphylococci, Meningococci, Pseudomonas, and Haemophilus influenzae./32/ It is seen in many clinical settings including Bruton's sex-linked recessive agammaglobulinemia, primary acquired agammaglobulinemia, lymphoproliferative diseases, especially chronic lymphocytic leukemia, thymoma intestinal lymphectasia, and following treatment with immunosuppressive agents. Cellular deficiency is characterized by cutaneous anergy, prolonged homograft survival, poor in vitro lymphocyte response to phytohemagglutinin (PHA), allogeneic cells, and antibody; frequent lymphopenia, and a propensity to infection

with low grade pathogens including the facultative intracellular pathogens such as tubercle bacilli, atypical acid-fast bacilli, Listeria, and Salmonella; fungi such as Candida and Cryptococcus; and viruses such as vaccinia, rubeola, and cytomegalic inclusion./32,33/ This disorder is seen in the congenital form in the Di George syndrome (also known as thymic aplasia), and in the acquired form associated with Hodgkin's disease, sarcoidosis, chronic renal insufficiency, and in patients receiving immunosuppressive agents.

COMMENT

Although the ventilatory and perfusion aspects of pulmonary function have preoccupied our attention, it should be recognized that the self-cleansing capacity of the lung plays as critical a role. With continuous inoculation of the pulmonary parenchyma with particles containing potential pathogens, an equilibrium between host and parasite is established based primarily on the efficient functioning of host defense mechanisms. In a wide variety of circumstances, only partially discussed in this paper, defenses are impaired and infection ensues.

References

1. Laurenzi GA, Potter RT, Kass EH: Bacteriologic flora of the lower respiratory tract. New Eng J Med 265:1273-1278, 1961
2. Green GM: Pulmonary clearance of infectious agents. Ann Rev Med 19:315-336, 1968
3. Green GM: The J. Burns Amberson Lecture. In defense of the lung. Amer Rev Resp Dis 102:691-703, 1970
4. Ammann AJ, Cain WA, Ishizaka K, et al: Immunoglobulin-deficiency in ataxia-telangiectasia. New Eng J Med 281:469-472, 1969

5. Yachnin S: Functions and mechanisms of action of complement. New Eng J Med 274:140-145, 1966
6. Weissmann G: Lysosomes. New Eng J Med 273:1084-1089, 1143-1149, 1965
7. Morgan TE: Pulmonary surfactant. New Eng J Med 284: 1185-1192, 1971
8. Merigan TC Jr: Interferon's promise in clinical medicine. Amer J Med 43:817, 821, 1967
9. Hatch TF: Distribution and deposition of inhaled particles in the respiratory tract. Conference on Airborne Infection. Bacteriol Rev 25:237-240, 1961
10. Brain JD: Free cells in the lung. Arch Intern Med 126: 477-487, 1970
11. Sorokin SP: Properties of alveolar cells and tissues that strengthen alveolar defenses. Arch Inter Med 126:450-463, 1970
12. Nagaishi C, Okada Y, Ishiko S, et al: Electron Microscopic observations of the pulmonary alveoli. Exp Med Surg 22:81-117, 1964
13. Fried BM: The lungs and the macrophage system. Arch Path 17:76-103, 1934
14. Moore RD, Schoenberg MD: Alveolar lining cells and pulmonary reticuloendothelial system of the rabbit. Amer J Path 45:991-1006, 1964
15. Pinkett MO, Cowdrey CR, Nowel PC: Mixed hematopoietic and pulmonary origin of "alveolar macrophages" as demonstrated by chromosome markers. Amer J Path 48:859-867, 1966
16. Heinemann HO, Fishmann AP: Nonrespiratory lung functions. Phys Rev 49:1-47, 1969
17. Ward PA, Lepow IH, Newman LJ: Bacterial factors chemotactic for polymorphonuclear leukocytes. Amer J Path 52:725-736, 1968
18. Douglas S: Disorders of phagocyte function. Blood 35:851-866, 1970
19. Klebanoff SJ: Myeloperoxidase-halide-hydrogen peroxide antibacterial system. J Bact 95:2131-2138, 1968
20. Simpson JF, Leddy JP, Hare JD: Listeriosis complicating lymphoma. Amer J Med 43:39-49, 1967
21. Lawrence HS: Transfer factor and cellular immune deficiency disease. New Eng J Med 283:411-419, 1970
22. Mandell GL, Hook EW: Leukocyte function in chronic granulomatous disease of childhood. Amer J Med 47:473-486, 1969

23. Quie PG, White JG, Holmes B, et al: Studies of the metabolic activity of leukocytes from patients with a genetic abnormality of phagocytic function. J Clin Invest 46:668-679, 1967
24. Douglas SD, Davis WG, Fudenberg HH: Granulocytopathies: Pleomorphism of neutrophil dysfunction. Amer J Med 46:901-909, 1969
25. Lehrer RI, Martin JC: Leukocyte myeloperoxidase deficiency and disseminated candidiasis. The role of myeloperoxidase in resistance to Candida infection. J Clin Invest 48: 1478-1488, 1969
26. Davis WC, Douglas SD, Fudenberg HH: A selective neutrophil dysfunction syndrome: Impaired killing of Staphylococci. Ann Intern Med 69:1237-1243, 1968
27. Green GM, Goldstein E: A method for quantitating intrapulmonary bacterial inactivation in individual animals. J Lab Clin Med 68:669-677, 1966
28. Green GM, Kass EH: The role of the alveolar macrophage in clearance of bacteria from the lung. J Exper Med 119:167-176, 1964
29. Green GM: Integrated defense mechanisms in models of chronic pulmonary disease. Arch Intern Med 126:500-503, 1970
30. Laurenzi GA, Guaneri JJ: Important determinants in pulmonary resistance to bacterial infection. Med Thorac 22:48-59, 1965
31. Good RA, Mazzitello WF: Chest disease in patients with agammaglobulinemia. Dis Chest 29:9-35, 1956
32. Gatti RA, Good RA: The immunologic deficiency diseases. Med Clin N Amer 54:281-307, 1970
33. Rosen FS: The lymphocyte and the thymus gland. Congenital and hereditary abnormalities. New Eng J Med 279:643-648, 1968

BLOOD GASES ARE PULMONARY FUNCTION TESTS!

LTC Edward E. Mays, MC

The most important function of the lungs is to supply the body with enough O_2 and to remove excess CO_2. In accomplishing this, the only two really important facilitating factors are (1) an adequate amount of alveolar ventilation and (2) adequate matching of the distribution of ventilation to pulmonary capillary perfusion. The only simple clinical laboratory method which detects abnormalities of these two factors is the determination of arterial blood gases.

Conventional pulmonary function testing has been used for many years to identify and to quantitate the numerous separate mechanical factors which contribute to the purely ventilatory activity of the lungs and chest bellows. Other indirect methods have been utilized in order to gain some insight into the ability of the lungs for efficiently handling gases and blood flow. Bronchospirometry and, more recently, radioactive scintiscans are methods employed to define the matching of ventilation to perfusion. While these techniques and others have contributed greatly to furthering the over-all understanding of respiratory physiology in health and disease, several basic realizations have emerged: (1) conventional function test results may bear little relationship to symptoms of disability or to blood gas test results in certain lung diseases, (2) commonly the conventional test results must be at least moderately deranged by most parameters in chronic obstructive pulmonary disease (COPD) and in restrictive lung disease before good correlation with symptoms result, and (3) significant blood gas derangement due to intrapulmonary disease may exist when conventional pulmonary function tests are completely normal. Most relevant pulmonary function testing has been removed from the realm of the clinician to that of the laboratory technologist. Filley /1/ has summarized the usefulness of standard pulmonary function tests as performed in the systematic study of the outpatient, and has alluded to the relative insensitivity of these tests. He also

indicates, unfortunately, that blood gas tests have little use in more routine function testing.

Recent improvements in the design of pulmonary function test equipment, usually by the addition of electronic sensors or computer readout, have removed some of the drudgery of setting up equipment and of calculating results, but no new useful information has been gained. The usefulness of blood gas test results has been repeatedly expounded in the recent pulmonary literature. At present such reports are concerned mostly with the management of respiratory failure, but with further clinical application of refinements of the ventilation-perfusion theory of Rahn and Farhi /2/, blood gas test results are assuming more of a favored position in the study of clinical pulmonary pathophysiology of outpatients. Pulmonary function tests on patients with severe disease are now rarely considered complete unless blood gas studies are also done. In fact, the diagnosis and management of severe pulmonary dysfunction are guided almost exclusively by blood gas test results. The arterial puncture has proved to be simple and safe, and the perfection of the pH and P_{O_2} electrodes have made the determinations rapid and accurate. One might therefore reasonably suggest that conventional pulmonary function testing has reached its peak of usefulness and that blood gas testing is in its ascendancy. I urge the more frequent use of blood gas tests along with, and in some cases instead of, routine function tests.

Background

The role of the lung as an oxygenator is limited to its capacity to maintain or modify the arterial oxygen tension (Pa_{O_2}). The oxygen quantity, saturation of hemoglobin, and the delivery system, all are effected by the Pa_{O_2}, however, their contributions to the study of tissue oxygenation are better reflected by other measurements. The Pa_{O_2}, however, has great relevance in the diagnosis and therapy of a wide variety of clinical conditions, and is becoming the most widely used measure of hypoxemia.

The level of the arterial carbon dioxide tension (Pa_{CO_2}) is a direct reflection of the efficiency of alveolar ventilation.

The $PaCO_2$ is normally kept from varying due to its scrupulous control by neural mechanisms. Its excretion from the body is not limited by the diffusion process (from blood to alveolar spaces) because of its high diffusability and the steep slope of its dissociation curve. The quantity factor for CO_2 transport is the bicarbonate ion, comprising 95 percent of the total CO_2 concentration in the blood.

Both PaO_2 and $PaCO_2$ may vary widely with the level of ventilation without greatly affecting the total blood content of either. For practical purposes, the $PaCO_2$ becomes elevated when alveolar ventilation is inadequate to its metabolic production, and depressed only when alveolar ventilation exceeds this level. On the other hand, the PaO_2 is reduced either with ineffective alveolar ventilation or with ventilation-perfusion mismatching. Uneven or mismatched alveolar ventilation in relationship to pulmonary capillary perfusion affects the PaO_2 much more than the $PaCO_2$. The PaO_2 is increased only by hyperventilation or by the inhalation of higher oxygen concentrations than exist in room air. A single blood gas test, therefore, provides information regarding the level and the efficiency of ventilation quickly, without significant discomfort, in any clinical situation.

Certain modifications of the blood gas test other than at rest are in clinical use, such as, while exercising, during various concentrations of oxygen breathing, and during voluntary hyperventilation. Although there is considerable overlapping of abnormalities in patients, each blood gas test furnishes additional practical clinical information in the individual case.

THE RESTING PaO_2 and $PaCO_2$

Sea-level resting PaO_2 (90 ± 3.5 mm Hg) and $PaCO_2$ (38 ± 1.1 mm Hg) indicate that the over-all ventilation/perfusion apparatus is functioning normally at the existing metabolic level, regardless of mechanical function test measurements to the contrary. The $PaCO_2$ is indirectly related to the pH, and directly related to the bicarbonate ion concentration. Since both these factors are more closely related to acid-base balance on a metabolic basis, and

although important in assessing the individual status, they will not be further discussed here.

Either PaO_2 or $PaCO_2$ may be either normal, low, or high at apparent rest, and the interrelationship of the two factors makes several combinations (nine) possible, although all do not concur. There are, of course, the same number of possible interrelationships at exercise, during hyperventilation, and during oxygen breathing. Control values for these tests are given in TABLE I.

It has been difficult to define precisely the "normal" resting arterial gas tensions.

Common values noted in the literature give "normal" broad ranges (PaO_2 80-100 mm Hg, $PaCO_2$ 35-45 mm Hg). As a result, the clinician is justified in erroneously concluding that a blood gas report which lists the PaO_2 as 100 mm Hg and the $PaCO_2$ as 45 mm Hg is a normal report. The following reasoning explains how this error might be made. The normal relationships of the PaO_2 to the $PaCO_2$, derived from my studies, are shown in Figure 1. It may be seen that the resting "normal" values outlined in the center of the figure comprise only a small portion of the possible normal axis, which here reflects the changes in gas tensions as related to the level of alveolar ventilation. Note the near-precise reciprocal relationship of PaO_2 to $PaCO_2$. When an individual with normal lungs is hyperventilating (for instance, due to metabolic acidosis or anxiety), and the $PaCO_2$ has been reduced to 20 mm Hg, it is "normal" for the PaO_2 to be 120 ($\pm$ 8) mm Hg, but not 90 mm Hg. Conversely, when an individual holds his breath, or has central nervous system depression, and the $PaCO_2$ is elevated to 52 mm Hg, it is "normal" for the PaO_2 to be 68 ($\pm$ 5) mm Hg, but not 50 mm Hg. As a memory crutch, for each 3.0 mm Hg that the $PaCO_2$ is reduced below its resting normal sea-level mean due to hyperventilation, the PaO_2 should be elevated about 5.0 mm Hg above its resting normal mean. For example, if the $PaCO_2$ is 33 mm Hg, the PaO_2 should be about 99 mm Hg. The reverse relationship also obtains to the same degree. See TABLE II for the predicted PaO_2 for any given $PaCO_2$ in normal subjects.

Since the $PaCO_2$ is a direct measure of effective ventilation, and the PaO_2 is a reflection of the effectiveness of

TABLE I
ARTERIAL BLOOD GAS CONTROL VALUES
(5 Controls, Non-smoking males; Mean ages 21; Height 71.4 in · BSA 2.026M^2)

	RESTING*	HYPERVENTILATION† 20 seconds	EXERCISE** 3 mph,3 degrees,5 min.	100% O_2 BREATHING* 15 minutes
PaO_2 mm Hg (mean)	**90**	**119**	**83**	**593**
Range	85 - 93	113 - 123	79 - 90	560 - 650
1 S.D.	3.5	8.2	5.4	37
Coefficient of Variation	3.9	6.9	6.4	6.2
P (paired comparison "t" test)		⟨ 0.01	N.S.	⟨ 0.001
Mean difference from resting		+28 (24 to 36)	-7 (+3 to -13)	+505 (473 to 563)
$PaCO_2$ mm Hg (mean)	**38.3**	**20.3**	**39.4**	**33**
Range	37 - 40	17 - 25	37 - 43	27 - 38
1 S.D.	1.1	3.2	2.7	4.4
Coefficient of Variation	2.87	15.8	6.78	13.3
P value ("t" test)		⟨ 0.01	N.S.	N.S.
Mean difference from resting		-18 (-15 to -22)	+1.6 (+3 to -1)	-5.2 (-1 to -11)
pH (mean)	**7.43**	**7.63**	**7.41**	**7.49**
Range	7.40 - 7.47	7.61 - 7.66	7.39 - 7.44	7.44 - 7.59
1 S.D.	0.075	0.056	0.075	0.086
P value ("t" test)		⟨ 0.01	N.S.	⟨ 0.01
Mean difference from resting		+0.21 (0.15 to 0.23)	-0.03 (+0.01 to -0.05)	+0.05 (0.03 to +0.15)
HCO_3 mEq/L (mean)	**25**	**21**	**25**	**24**
Range	22.5 - 28.5	17 - 25	22 - 27.5	21 - 25.5
1 S.D.	2.4	. . .	. . .	. . .
P value ("t" test)		0.05 - 0.02	N.S.	N.S.
Mean difference from resting		4	0	1

* = supine † = sitting ** = treadmill ( ) = range N.S. = not significant

TABLE II

PREDICTED PaO_2 FOR ANY GIVEN $PaCO_2$ IN NORMAL SUBJECTS

$PaCO_2$	PREDICTED PaO_2*	$PaCO_2$	PREDICTED PaO_2*
mm Hg	mm Hg	mm Hg	mm Hg
45	79	31	102
44	81	30	104
43	82	29	105
42	84	28	107
41	86	27	108
40	86	26	110
39	89	25	112
38	91	24	113
37	92	23	115
36	94	22	116
35	96	21	118
34	97	20	120
33	99	19	122
32	101	18	124

*Values rounded off to nearest whole number, and calculated from the following

Regression formula for $PaCO_2$ below 40 mm Hg:
$PaO_2 = 150.63 - 1.57 (PaCO_2)$

Regression formula for $PaCO_2$ above 40 mm Hg:
$PaO_2 = 152.9 - 1.64 (PaCO_2)$

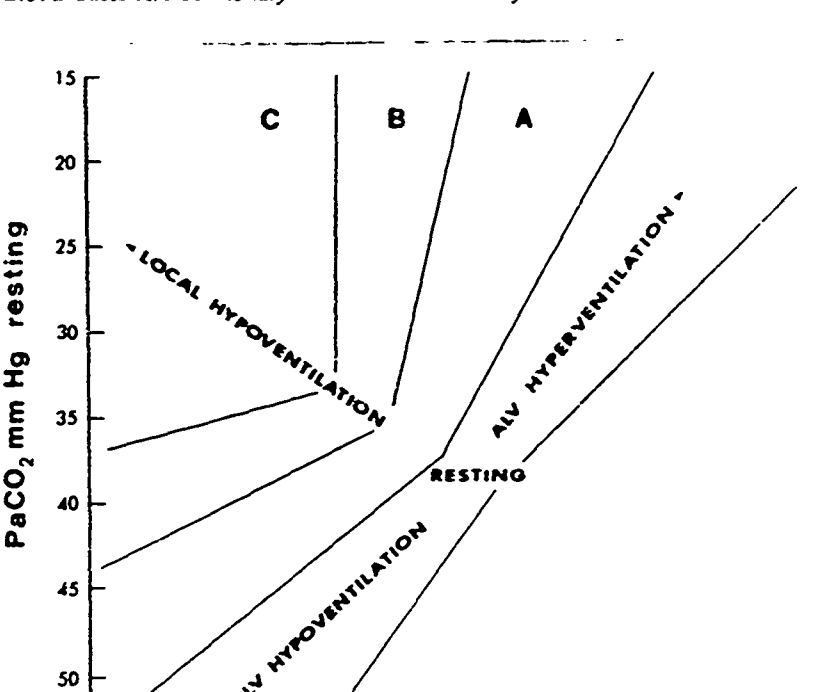

Fig. 1. PaO_2 - $PaCO_2$ diagram. Normal values (± SD) enclosed in the right-sided diagonal space, with centrally located resting values flanked by alveolar hyperventilation (upper right) and hypoventilation (lower right). "Local" hypoventilation, extending from center to upper left, reflects increasing A-aDO_2 or $\dot{V}/\dot{Q}$ mismatching. Spaces A, B, and C are arbitrarily labeled, and enclose 2, 4, and 6 standard deviations, respectively, from the normal axis.

perfusion, a simple ventilation-perfusion ($\dot{V}/\dot{Q}$) relationship can be derived from blood gases alone. In an individual patient, the deviation of the observed PaO_2 from the predicted PaO_2 for that observed $PaCO_2$ is a measure of this $\dot{V}/\dot{Q}$ defect. The normal resting gas tensions, therefore, must be defined, and applied clinically in relationship to each other, never separately.

The most frequent initial blood gas test result in ambulatory pulmonary patients, as relates to the PaO_2 - $PaCO_2$ axis, is a low PaO_2 (hypoxemia) with a low $PaCO_2$ (hypocarbia). This fact is evident or recognized to occur in a number of acute conditions such as asthma /3/, peritonitis

or ileus /4/, acute diffuse interstitial lung disease due to several causes /5/, and blunt chest trauma /6/. In a few instances when disease is mild, (and perhaps the earliest clinically measureable indication of lung disease) the PaO_2 may be maintained in the "normal" range by reflex hyperventilation, reflected by a lowered $PaCO_2$. This hyperventilation is not usually abolished by oxygen breathing, proving that hypoxemia is not the etiology. Hypocarbia with normal or slightly lowered PaO_2 levels is also frequently noted in stable, mildly severe chronic conditions such as chronic obstructive pulmonary disease /7/, and in other nonspecific thoracic conditions /8/. This blood gas abnormality is associated with an increased alveolar-arterial O_2 difference ($AaDO_2$), shown in Figures 2 and 3 as leftward deviations of

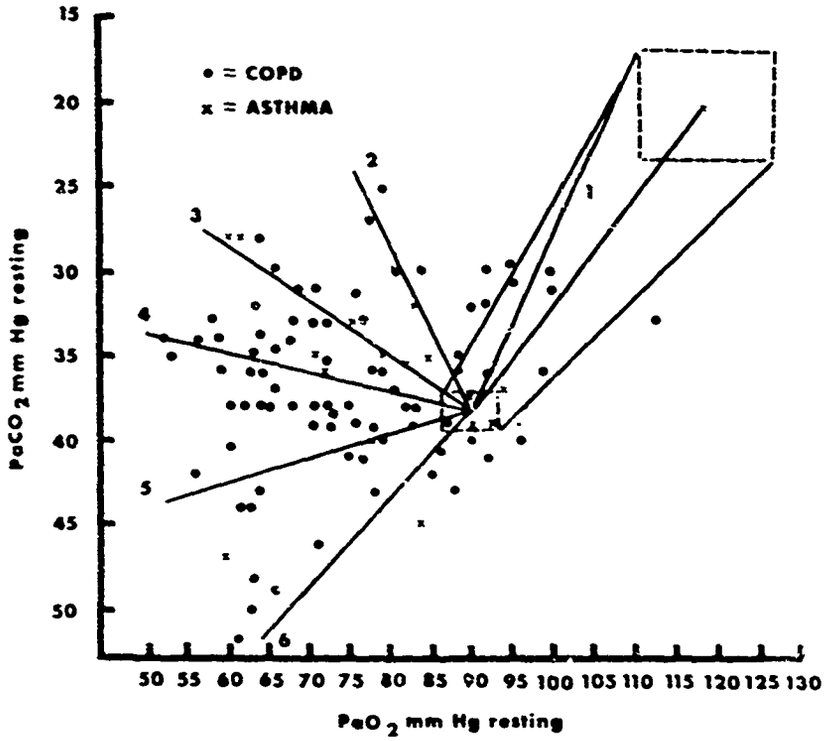

Fig. 2. PaO_2 - $PaCO_2$ diagram (partial) showing resting gas tension values obtained from subjects with obstructive airways diseases.

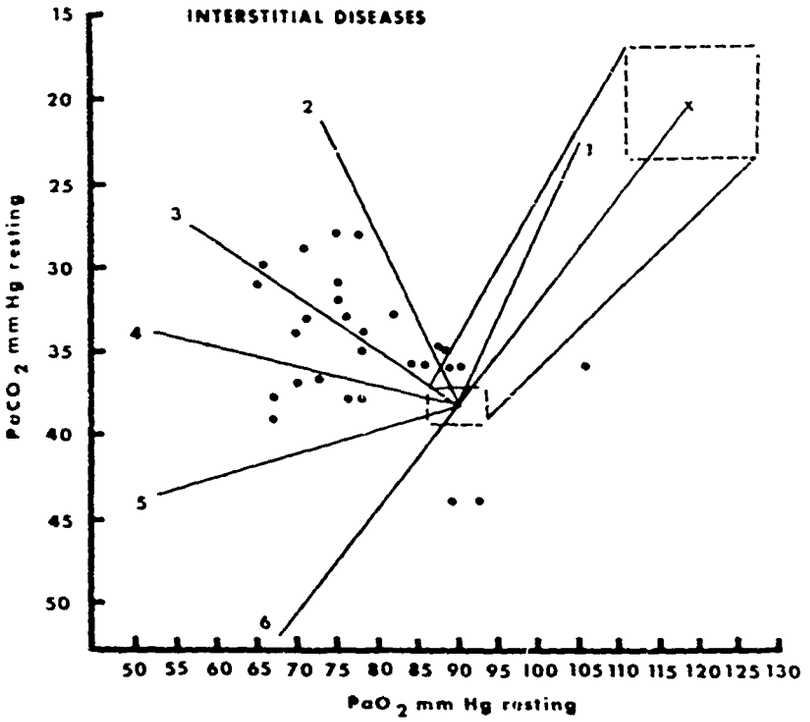

Fig. 3. PaO_2 - $PaCO_2$ diagram (partial) showing resting arterial gas tensions obtained from subjects with restrictive or diffuse infiltrative lung diseases.

the resting PaO_2 away from the normal axis (i.e., away from the predicted PaO_2 for a given $PaCO_2$). The decreased PaO_2 in such cases is directly related to the severity of expiratory airways obstruction in chronic obstructive pulmonary disease (COPD) and asthma, and to the restricted lung volumes and reduced compliance in restrictive lung diseases /8/, and is indirectly related to the amount of wasted ventilation in pulmonary vascular disease /9/.

In all these conditions, the $PaCO_2$ is directly related to the magnitude of alveolar ventilation. In mild disease, the $PaCO_2$ is generally below normal, and becomes progressively lower as the disease worsens. However, when the work of breathing and metabolic CO_2 output increase to the point where alveolar ventilation is mandatorily reduced, the $PaCO_2$ gradually reverts toward normal and eventually to hypercapnia./2,7,8/ This "crossover" of the $PaCO_2$ from

hypocapnia to hypercapnia tends to occur insidiously as COPD worsens, and is usually accompanied by renal retention of HCO_3 ion, thus maintaining a normal blood pH. In acute respiratory failure due to any cause, but especially in asthma and interstitial lung diseases, the crossover usually reflects a serious, acute deterioration in the patient's condition and prognosis. Acute CO_2 retention cannot be rapidly compensated for by body buffer mechanisms or by renal compensation. Unless O_2 is given the patient, hypoxemia concurrently worsens as well, a condition also tolerated poorly, needless to say.

With severe degrees of disease of either major category (obstructive or restrictive), the lowered resting Pa_{O_2}, primarily due to $\dot{V}/\dot{Q}$ disturbances, is contributed to by intrapulmonary shunt-like effects or by actual shunting of pulmonary capillary perfusion past hypoventilated or unventilated alveoli. (This is amplified in the section on oxygen breathing Pa_{O_2}.) Shunting must also be considered a severe $\dot{V}/\dot{Q}$ abnormality in lung disease, rather than a separate mechanism for hypoxemia.

THE EXERCISING Pa_{O_2} and Pa_{CO_2}

The results of blood gases obtained during exercise are difficult to interpret for several reasons. It is generally believed that exercise places stress upon both the pulmonary and cardiac contributions to the over-all gaseous exchange mechanism, but that the blood gas disturbance produced is particularly representative of a decreased pulmonary capillary reserve, or of a lowered cardiac response to stress. It is presumed by some, and questioned by others, that an attenuated pulmonary capillary bed attendant to disease cannot accept the increased cardiac output associated with exercise without seriously increasing the transit time of the pulmonary capillary blood flow. This in turn decreases the duration of red blood cell contact at the alveolar-capillary membrane, limiting the oxygen exchange efficiency and ultimately causing systemic arterial hypoxemia.

It is difficult, however, to separate the pulmonary from the cardiac contributions and compensations in test

results. Other difficulties encountered in the use of exercise blood gas test results include (1) estimation of the influence of metabolic products (or reflexes secondary to them, such as hyperventilation) on the blood gas tensions, (2) establishment of the optimal level of physical exertion for each individual and the subsequent problems in comparing the results between individuals, (3) the proper vehicle upon which exercise should be performed (bicycle, ergometer, treadmill or steps), (4) the influence of prior training or exercise testing upon the work tolerance and muscular efficiency of the individual; and others.

The mean exercise blood gas tensions in normal subjects remain reasonably close to those obtained at rest. Individuals, however, may show small changes in either direction. About 20 percent of patients who have mild COPD or diffuse parenchymal diseases, manifested by a small decrease in resting PaO_2, will further decrease the PaO_2 during exercise. This percentage gradually increases to 100 percent with increasing severity of disease./10/ The $PaCO_2$ may remain stationary, rise, or decrease with exercise, depending on the level of ventilation reached and the metabolic CO_2 production. A marked increase in $PaCO_2$ presupposes worsened alevolar ventilation in relation to the work output, hence an inability of the gas exchange apparatus to meet the increased metabolic production of CO_2. Respiratory muscles themselves may be responsible for most of this added CO_2 production (and simultaneously increased oxygen utilization) when the work of breathing is much increased. Airflow resistance secondary to narrowed airways, and restriction or stiffness of the lungs or thoracic cage are general examples of causes of increased work of breathing.

HYPERVENTILATING P_2O_2 and $PaCO_2$

This test reflects most of the factors represented in the resting gas tensions, however, the imposed activity makes it a stress test of the predominantly ventilatory function of the gas exchange apparatus. In this sense it is comparable to the exercise test which, as we have discussed, is thought to be a stress test of the pulmonary capillary perfusion apparatus.

The normal subject at sea-level can, by voluntary hyperventilation for 20 seconds, decrease his $PaCO_2$ to 20 (± 2) mm Hg and elevate his PaO_2 to 120 (± 8) mm Hg./8,11/ This short duration of hyperventilation makes this test relatively independent of cardiac factors, and makes side effects unlikely, unlike the exercise tests.

About 80 percent of patients with COPD or diffuse lung diseases who have a low resting PaO_2 cannot normally raise the hyperventilating PaO_2./8/ The ability to do so decreases as the disease process worsens, regardless of etiology.

The present usefulness of this test is largely limited to the evaluation of central nervous system-induced alveolar hypoventilation. In such cases, voluntary hyperventilation produces a normal or near normal response in arterial gas tensions if the lungs function normally. In severe COPD, frequently neither the PaO_2 nor the $PaCO_2$ change significantly with voluntary hyperventilation, probably indicating that no real increase in alveolar ventilation occurs, despite the increased effort. In less severe COPD and other types of lung disease, however, the $PaCO_2$ may change significantly /8,11/, while the PaO_2 does not, a reflection of altered $\dot{V}/\dot{Q}$ relationships. As outlined above, the degree of failure of the PaO_2 change to correlate with the $PaCO_2$ is a simple measure of the severity of over-all V/Q mismatching./10/ The degree of failure of the $PaCO_2$ to reach expected levels is a simple measure of the severity of the decrease in ability to ventilate effectively.

THE OXYGEN-BREATHING PaO_2 and $PaCO_2$

A uniformly observed gradient exists between the PO_2 of alveolar air and that of arterial blood in normal subjects. This difference, the alveolar-arterial oxygen tension difference ($A\text{-}aDO_2$), reflects in part the percentage of the cardiac output which passes from the right to the left side of the heart without contacting or becoming equilibrated with alveolar gas. A right-to-left shunt in congenital heart disease produces such a difference, for example. In normal subjects, up to three percent of the cardiac output shunts past the

alveolar membrane /12/, which itself presents a small (but measureable) resistance to oxygen diffusion /13/. The resultant mixed arterialized blood leaving the lungs is diluted by shunted venous blood and fails to reach the PO_2 of alveolar gas. This true venous shunting comprises the anatomical shunt, which includes blood from thebesian veins and blcod which traverses the lung, but completely bypasses alveoli or perfuses nonventilated alveoli (via, for example, bronchopulmonary anastomosis). Exaggerated in diseased subjects, an additional shunt, the virtual shunt, arises from the inadequate ventilation of certain parts of the pulmonary capillary flow (unequal distribution of $\dot{V}A$ to Q). Although this is not a true shunt, the effect of admixture with arterialized blood is the same, that is to increase the $A\text{-}aDO_2$ and thereby decrease the PaO_2. The percentage of shunting (Qs/Qt percent) can be calculated by the shunt equation. This formula may be used to calculate the fraction of the cardiac output shunted from the venous to the arterial circulation without contact with functional alveolar spaces. /12/ This formula is valid if patient is breathing a known high concentration of oxygen that causes the hemoglobin to be completely saturated.

$$\frac{Qs}{Qt} = \frac{(P_{AO_2} - PaO_2)\,0.003}{(P_{AO_2} - PaO_2)\,0.003 + A\text{-}vO_2 \text{ difference}}$$

Qs	=	Flow of shunted blood
Qt	=	Total cardiac output
P_{AO_2}	=	Alveolar oxygen tension ($P_B - P_{H2O} - PaCO_2$)
PaO_2	=	Arterial oxygen tension
0.003	=	Solubility factor for oxygen at 37° C expressed as ml per mm Hg per 100 ml blood.
$A\text{-}vO_2$	=	Difference in O_2 content in ml/100 ml blood between arterial and mixed venous blood (assumed to be 5 vol % at rest).

Normal subjects breathing 100 percent oxygen for 15 minutes at sea-level will increase the $Pa0_2$ from 90 mm Hg up to the range of 625 mm Hg. The simultaneous alveolar oxygen tensions change from about 100 mm Hg to the range of 655 mm Hg. The $PaCO_2$ normally falls about 15 percent due to reflex hyperventilation attendant to oxygen breathing. The $A\text{-}aDO_2$ on room air in normals then is about 10 mm Hg, and on 100 percent oxygen is about 30 mm Hg./12,14/ In normal persons over 60 years old, these gradients are each approximately doubled, in keeping with the known anatomic changes which occur in the lungs with aging./15/

The clinical importance of the $A\text{-}aDO_2$ during 100 percent oxygen breathing is in its reflection of the total shunting, hence the severity of the VA/Q mismatching in diseased lungs. TABLE III.

TABLE III

CORRESPONDING $A\text{-}aDO_2$ and Qs/Qt FOR A GIVEN $Pa0_2$ DURING 100% 0_2 BREATHING FOR 15 MINUTES AT SEA LEVEL

$Pa0_2$	$A\text{-}aDO_2$	Qs/Qt
mm Hg	mm Hg	Percent
632	40	2.3
612	60	3.5
592	80	4.6
572	100	5.6
552	120	6.7
532	140	7.7
512	160	8.7
492	180	9.7
472	200	10.7
452	220	11.6
432	240	12.6
412	260	13.5
392	280	14.4
372	300	15.2

$A\text{-}aDO_2$ = alveolar-arterial oxygen difference
Qs/Qt = ratio of shunted blood to total pulmonary blood flow

COMMENT

Since the primary function of the lungs is that of gaseous exchange, pulmonary function tests which do not include the determination of blood gases are measures of lesser factors. Standard function tests are cumbersome, most are insensitive and of limited relevance, and collectively, they often fail to detect significant disease by being false-positive or false-negative.

Blood gas tests have proved to be of unquestioned value in the diagnosis and management of the severest forms of pulmonary dysfurction, and in such circumstances qualify as the "ultimate" in function testing. Yet, they remain sensitive enough, properly interpreted, to detect some of the earliest pathophysiologic changes incident to lung disease. They appear to correlate with prognosis better than any standard pulmonary function test or combination of them.

Blood gas test results are always relevant, regardless of the category of lung disease, and are easily adaptable to stress testing of the subject. A single blood gas test provides supplementary information about lung function that is not otherwise available, except by inference. Arterial punctures are simple and safe and may be repeated whenever necessary. It is recommended that blood gas tests be used more frequently in pulmonary function testing.

References

1. Filley GF: Pulmonary insufficiency and respiratory failure. Philadelphia, Lea & Febigir, 1967, p 59
2. Rahn H, Farhi LE: Ventilation, perfusion and gas exchange: The $\dot{V}/\dot{Q}$ concept. Handbook of Physiology. Washington, D.C.: American Physiological Society, Vol 1, Sec 3, 1964
3. McFadden ER Jr, Lyons HA: Arterial-blood gas tensions in asthma. New Eng J Med 278:1027, 1968
4. Burke JF, Pontoppidan H, Welch CE: High output respiratory failure. An important cause of death ascribed to peritonitis or ileus. Ann Surg 158:581, 1963
5. Ashbough DG, Bieglow DB, Petty TL, et al: Acute respiratory distress in adults. Lancet 2:319, 1967
6. Wise AJ, Topuzlu C, Mills EL, et al: The importance of serial blood gas determinations in blunt chest trauma. J Thorac Cardiovasc Surg 56:520,1968
7. Lourenco RV, Miranda JM: Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. New Eng J Med 279:53, 1968
8. Mays EE: An arterial blood gas nomogram for clinical use. Submitted for publication
9. Nadel JA, Gold WM, Burgess JH: Early diagnosis of chronic pulmonary vascular obstruction: Value of pulmonary function tests. Amer J Med 44:16, 1968
10. Mays EE: The arterial oxygen tension during voluntary hyperventilation. Comparison with other pulmonary function tests. Presented at the 23d Annual Pulmonary Disease Symposium, Fitzsimons General Hospital, Denver Colorado, September 17, 1970
11. Rotsztain A, Haddad R, Canter HG: Blood gas changes during voluntary hyperventilation in normal and disease states. Amer Rev Resp Dis 102:205, 1970
12. Ayres SM, Criscitiello A, Grabovsky E: Components of alveolar-arterial O_2 difference in normal man. J Appl Physiol 19(1):43, 1964
13. Riley RL, Cournand A: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: Theory. J Appl Physiol 4:77, 1951

14. Cole RB, Bishop JM: Variation in alveolar-arterial O_2 tension difference at high levels of alveolar O_2 tension. J Appl Physiol 22(4):685, 1967
15. Kanber GJ, King FW, Eschar YR, et al: The alveolar-arterial gradient in young and elderly men during air and oxygen breathing. Amer Rev Resp Dis 97:376, 1968

ACKNOWLEDGEMENT

Mrs. Louise Love, secretary to the Chief Pulmonary and Infectious Diseases, typed the narratives of this entire symposium. She unselfishly gave of her time in the evenings and on the weekends so as to prepare these papers in addition to her regular duties.